Supreme Court of the United States

OCTOBER TERM, 1965

No. 58

EDWARD J. BRENNER, COMMISSIONER OF PATENTS, PETITIONER

vs.

ANDREW JOHN MANSON

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS

INDEX

IN THE UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS

PATENT APPEAL DOCKET
No. 7140

IN THE MATTER OF THE APPLICATION OF ANDREW JOHN MANSON

APPEAL FROM BOARD OF APPEALS

---

* * * *

[fol. 1]

* * * *

Applicant: Andrew John Manson; Serial 3,693; Filed: 1960 January 20; For: PREPARATION OF 2-METHYL-17α-LOWER-ALKYLANDROSTAN-17β-OL-3-ONES

PETITION OF APPEAL UNDER RULE 25—filed February 5, 1963

To the United States Court of Customs and Patent Appeals:

Your petitioner, Andrew John Manson, of the Town of North Greenbush, County of Rensselaer, State of New York, respectfully represents:

That he is the original and first inventor of certain new and useful improvements in Preparation of Organic Compounds (Title amended to: Preparation of 2-Methyl-17α-Lower-Alkylandrostan-17β-Ol-3-Ones).

That on the 20th day of January 1960, in the manner prescribed by law, he presented his application to the Patent Office, praying that a patent be issued to him for the said invention.

That such proceedings were had in said Office upon said application;

That on the 26th of September 1962 an adverse decision was rendered by the Board of Appeals affirming the rejection of the Primary Examiner and a patent for said invention as embodied in claims 2 and 3 was refused him.

That on the 23rd day of November 1962, your petitioner, pursuant to Section 142 of Title 35, United States Code, gave notice to the Commissioner of Patents of his appeal to this honorable court of his refusal to issue a [fol. 2] patent to him for said invention upon said application as aforesaid, and filed with him in writing, the special reasons of appeal hereinafter included.

That on 1963 January 9 the Commissioner of Patents extended the time for filing this Petition of Appeal until 1963 February 11.

That the Commissioner of Patents has furnished him a certified transcript of the record and proceedings relating to said application for patent, including the notice and reasons of appeal, which transcript is being transmitted to this court directly by the Patent Office for filing herewith and is to be deemed and taken as a part hereof.

Wherefore your petitioner prays that his said appeal may be heard upon and for the reasons assigned therefore to the Commissioner as aforesaid, and that said appeal may be determined and the decision of the Commissioner be revised and reversed, that justice may be done in the premises.

A check for the filing and docketing fee, in the amount of Fifteen Dollars ($15.00) is attached.

ANDREW JOHN MANSON

By LAURENCE AND LAURENCE
753 Warner Building
Washington 4, D. C.
Attorneys for Manson

Of Counsel:

DEAN LAURENCE
HERBERT I. SHERMAN

[File Endorsement Omitted]

CERTIFICATE OF COMMISSIONER OF PATENTS TO RECORD

U. S. DEPARTMENT OF COMMERCE
UNITED STATES PATENT OFFICE

February 4, 1963
(Date)

THIS IS TO CERTIFY that the annexed is a true copy from the records of this office of Certain Requested Docu-
[fol. 3] ments, said Documents being the Record for the United States Court of Customs and Patent Appeals, in the matter of the

Pending Application of
Andrew John Manson,

Filed January 20 1960, Serial Number 3,693,
for
Preparation of 2-Methyl-17α-Lower-Alkylandrostan-17β-ol-3-Ones.

By authority of the
COMMISSIONER OF PATENTS

W. G. LANHAM JR.
(SEAL) Certifying Officer.

APPLICATION OF ANDREW JOHN MANSON, FILED JANUARY 20, 1960, SERIAL NUMBER 3,693, FOR PREPARATION OF ORGANIC COMPOUNDS

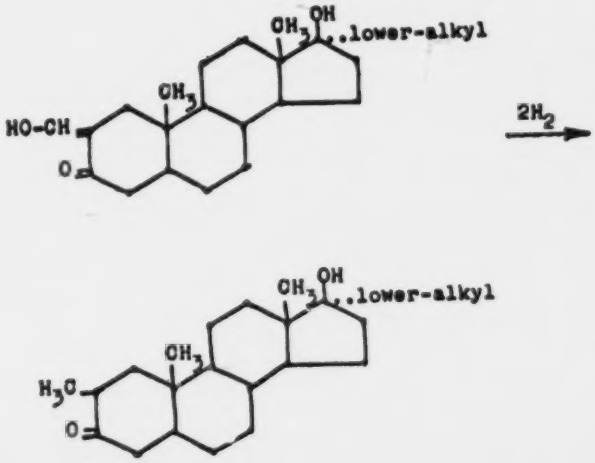
This invention relates to a new method of preparation of 2-methyl-17α-lower-alkylandrostan-17β-ol-3-ones (2-methyl-17α-lower-alkyl-dihydrotestosterones). The method comprises catalytically hydrogenating a 2-hydroxymethylene-17α-lower-alkylandrostan-17β-ol-3-one.

The known method for preparing 2-methyl-17α-lower-alkylandrostan-17β-ol-3-ones from the corresponding 17α-lower-alkylandrostan-17β-ol-3-ones involves several steps, e.g., introducing an ethoxyoxalyl group into the 2-position by reacting the 3-oxo-steroid with ethyl oxalate in the presence of a strong base, methylating with methyl iodide,

and finally cleaving the ethoxyoxalyl group by reversal of the oxalate condensation.

It has now been found that the introduction of the 2-methyl group can be realized in a fewer number of steps by introducing a hydroxymethylene group into the 2-position by reacting a 17α-lower-alkylandrostan-17β-ol-3-one [fol. 4] with a lower-alkyl formate in the presence of a strong base, e.g., sodium methoxide or sodium hydride, under anhydrous conditions and then catalytically hydrogenating the hydroxymethylene derivative whereby the double bond is reduced and the terminal hydroxy group is replaced by hydrogen. This is equivalent to the reduction of a formyl (O=CH—) group to a methyl group.

[fol. 5]



The hydrogenation process of the invention takes place at ordinary temperatures and at atmospheric or slightly elevated pressure in an inert solvent. The catalyst employed can be any of those known to reduce formyl groups to methyl groups and includes such catalysts as palladium, e.g., palladium on carbon and palladium hydroxide on strontium carbonate, or platinum, e.g., platinum oxide.

Stereochemical considerations indicate that the hydrogenation of the 2-hydroxymethylene steroid initially produces a 2-methyl group in the β-configuration which has the unstable, axial conformation. During purification procedures, however, especially if alkaline treatment is involved, the product is largely epimerized to the 2α-methyl configuration having the stable, equatorial conformation.

The alkyl group in the 17α-position preferably has from one to about three carbon atoms and thus includes methyl, ethyl, propyl and isopropyl.

[fol. 7] The following examples will further illustrate the invention without limiting the latter thereto.

Example 1

(a) *2-Hydroxymethylene-17α-methylandrostan-17β-ol-3-one.*

A solution of 20.7 g. of 17α-methylandrostan-17β-ol-3-one in 500 ml. of benzene was added to sodium methoxide (prepared by dissolving 15.0 g. of sodium in 250 ml. of absolute methanol, concentrating the solution and drying the residue for one hour at 150-160°C. and 15 mm.). Ethyl formate (48.8 g.) was then added with stirring in a nitrogen atmosphere. The reaction mixture was stirred for four hours longer at room temperature, allowed to stand for about fifteen hours, stirred for two hours longer and then poured into water. The benzene layer was separated and the aqueous layer extracted with benzene. Nitrogen was bubbled through the aqueous layer to remove benzene, and the mixture was filtered. Concentrated hydrochloric acid and ice were added to the filtrate until the mixture was acid to Congo Red, and the product was extracted with chloroform. The chloroform extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a volume of 80 ml., whereupon there separated 14.89 g. of 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one, m.p. 179-183°C. (uncorr.). A sample when recrystallized from an ether-methanol mixture and dried at 80°C. *in vacuo* had the m.p. 185-190.5°C.(corr.), $[\alpha]_D^{25}=+22.3°$ (1% in chloroform); ultraviolet maximum at 282 mμ (E=10,300).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70.
Found: C, 76.10; H, 9.53.

(b) *2α,17α-Dimethylandrostan-17β-ol-3-one.*

2-Hydroxymethylene-17α-methylandrostan-17β-ol-3-one (4.00 g.) was dissolved in 200 ml. of 95% ethanol, 0.50 g. [fol. 8] of 22% palladium hydroxide on strontium carbonate catalyst was added, and the mixture was subjected to hydrogenation at room temperature and about 50 lbs. per sq. in. pressure. After about one and one-half hours

two molecular equivalents of hydrogen had been absorbed, and the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* on a steam bath, the residue was dissolved in ethyl acetate and a little ether, and the solution filtered free of a fine suspension and concentrated to dryness *in vacuo*. The residue (4.09 g.) was dissolved in a benzene-pentane (1:1) mixture and subjected to chromatography on 140 g. of acid-washed alumina. The column was eluted with 44 400 ml. portions of benzene-pentane (1:1). The crystalline material (1.91 g., m.p. 121-136°C.) obtained from fractions 4 to 44 was recrystallized successively from ether-pentane, methanol-water, and ether-pentane and dried for eight hours at 95°C. *in vacuo* to give 2α,17α-dimethylandrostan-17β-ol-3-one in the form of colorless plates, m.p. 138.6-142.4°C. (corr.), $[\alpha]_D^{25}$ $=+8.82° \pm 0.2°$ (1% in chloroform); infrared maxima at 2.92 and 5.85 μ, and a shoulder at 5.86μ indicating the possible presence of some of the 2β-methyl stereoisomer.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76.
Found: C, 79.10; H, 10.65.

Example 2

2α-Methyl-17α-ethylandrostan-17β-ol-3-one can be prepared by replacing the 17α-methylandrostan-17β-ol-3-one in Example 1, part (a) by a molar equivalent amount of 17α-ethylandrostan-17β-ol-3-one.

Example 3

2α-Methyl-17α-propylandrostan-17β-ol-3-one can be prepared by replacing the 17α-methylandrostan-17β-ol-3-one in Example 1, part (a) by a molar equivalent amount of 17α-propylandrostan-17β-ol-3-one.

[fol. 9] *Example 4*

2α-Methyl-17α-isopropylandrostan-17β-ol-3-one can be prepared by replacing the 17α-methylandrostan-17β-ol-3-one in Example 1, part (a) by a molar equivalent amount of 17α-isopropylandrostan-17β-ol-3-one.

* * * *

For Claim 2, see Rejected Claim 2.

Oath, Power of Attorney, and Petition

Being duly sworn, I, ANDREW JOHN MANSON

depose and say that I am a citizen of Canada residing at Town of North Greenbush, Rensselaer County, New York; that I have read the foregoing specification and claims and I verily believe I am the original, first, and sole inventor of the invention in PREPARATION OF ORGANIC COMPOUNDS

described and claimed therein; that I do not know and do not believe that this invention was ever known or used before my invention thereof, or patented or described in any printed publication in any country before my invention thereof, or more than one year prior to this application, or in public use or on sale in the United States more than one year prior to this application; that this invention has not been patented in any country foreign to the United States on an application filed by me or my legal representatives or assigns more than twelve months before this application; and that no application for patent on this invention has been filed by me or my representatives or assigns in any country foreign to the United States, except as follows:

NONE

And I hereby appoint Elmer J. Lawson, B. Woodrow Wyatt, Thomas L. Johnson, Robert K. Bair, and R. Clifford Bourgeois, Registry Nos. 15,355, 16,521, 16,687, 16,893, and 18,871, respectively, all c/o Sterling-Winthrop Research Institute, Rensselaer, New York, or any of them my attorneys or agents with full power of substitution and revocation to prosecute this application and to transact all business in the Patent Office connected therewith; and request that all communications be addressed to the said Elmer J. Lawson.

Wherefore I pray that Letters Patent be granted to me for the invention described and claimed in the foregoing specification and claims, and I hereby subscribe my name to the foregoing specification and claims, oath, power of attorney, and this petition, this

18th day of January, 1960.

Inventor Andrew (First name) John (Middle initial) Manson (Last name)

Post Office Address { Box 126B
R.D. 1
Rensselaer, New York

State of New York
County of Rensselaer } ss

Before me personally appeared Andrew John Manson *to me known to be the person described in the above application for patent, who signed the foregoing instrument in my presence, and made oath before me to the allegations set forth therein as being under oath, on the day and year aforesaid.*

[SEAL]

Anna C. Card
Notary Public

ANNA C. CARD
Notary Public, State of New York
Qualified in Albany County
Commission Expires March 30, 1961

[fol. 13]

AFFIDAVIT OF MANSON, DATED JANUARY 18, 1960

State of New York)
) ss.:
County of Rensselaer)

I, ANDREW JOHN MANSON, being duly sworn, depose and say:

THAT I am a citizen of Canada, residing at Town of North Greenbush, County of Rensselaer, State of New York;

THAT I am the applicant in the above-identified application, filed of even date herewith, under Agents' Docket Designation D.N. 4323;

THAT I made the invention described in the above-identified application in the United States of America prior to December 17, 1956, the priority date of U.S. Patent 2,908,693, issued October 13, 1959 to Syntex S.A., assignee of Howard J. Ringold and George Rosenkranz:

And further I say not.

ANDREW JOHN MANSON

Sworn to and subscribed before me this 18th day of January, 1960.

ANNA C. CARD
Notary Public, State of New York
Qualified in Albany County
(SEAL) Commission Expires March 30, 1960

LETTER REQUESTING AMENDMENT, DATED MARCH 31, 1960

Hon. Commissioner of Patents
Washington 25, D. C.

Sir:

In response to the Office Letter of March 10, 1960, please amend the above-identified application as follows:

Change the title to read: —PREPARATION OF 2-METHYL-17α-LOWER-ALKYLANDROSTAN-17β-OL-3-ONES—.

* * * *

[fol. 14] *REMARKS*

* * * *

Respectfully submitted,

ANDREW JOHN MANSON

By THOMAS L. JOHNSON
His Agent

March 31, 1960

AFFIDAVIT OF MANSON, DATED MARCH 30, 1960

State of New York)
) ss.:
County of Rensselaer)

I, ANDREW JOHN MANSON, being duly sworn depose and say:

THAT I am a citizen of Canada, residing at Town of North Greenbush, County of Rensselaer, State of New York;

THAT I am the applicant in the above-identified U. S. patent application, Serial No. 3693, filed January 20, 1960;

THAT I made the invention described in the above-identified application in the United States of America prior to December 17, 1956, the priority date of U.S.

Patent 2,908,693, issued October 13, 1959 to Syntex S.A., assignee of Howard J. Ringold and George Rosenkranz, as evidenced by the following acts:

THAT, prior to December 17, 1956, I prepared 2-hydroxy-methylene-17α-methylandrostan-17β-ol-3-one as follows, this procedure being the same as described in Example 1(a) at page 3 of the above-identified application: A solution of 20.7 g. of 17α-methylandrostan-17β-ol-3-one in 500 ml. of benzene was added to sodium methoxide (prepared by dissolving 15.0 g. of sodium in 250 ml. of absolute methanol, concentrating the solution and drying the residue for one hour at 150-160°C. and 15 mm.). Ethyl formate (48.8 g.) was then added with stirring in a nitrogen atmosphere. The reaction mixture was stirred for four hours longer at room temperature, allowed to [fol. 15] stand for about fifteen hours, stirred for two hours longer and then poured into water. The benzene layer was separated and the aqueous layer extracted with benzene. Nitrogen was bubbled through the aqueous layer to remove benzene and the mixture was filtered. Concentrated hydrochloric acid and ice were added to the filtrate until the mixture was acid to Congo Red, and the product was extracted with chloroform. The chloroform extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a volume of 80 ml., whereupon there separated 14.89 g. of 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one, m.p. 179-183°C. (uncorr.). A sample when recrystallized from an ether-methanol mixture and dried at 80°C. *in vacuo* had the m.p. 185-190.5°C. (corr.), $[\alpha]_D^{25}=+22.3°$ (1% in chloroform); ultraviolet maximum at 282 mμ (E=10,300).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70.
Found: C, 76.10; H, 9.53.

THAT the attached Exhibits A and B are photocopies of pages 155 and 157, respectively, of my notebook Man-A kept in the ordinary course of business and in my handwriting. The entries appearing in this notebook record were made prior to December 17, 1956. Exhibits A and

B show the preparation of 2-hydroxy-methylene-17α-methylandrostan-17β-ol-3-one by the above-described procedure;

THAT, prior to December 17, 1956, I prepared 2α,17α-dimethylandrostan-17β-ol-3-one as follows, this procedure being the same as described in Example 1(b) at page 4 of the above-identified application: 2-Hydroxymethylene-17α-methylandrostan-17β-ol-3-one (4.00 g.) was dissolved in 200 ml. of 95% ethanol, 0.50. g. of 22% palladium hydroxide on strontium carbonate catalyst was added, and the mixture was subjected to hydrogenation at room temperature and about 50 lbs. per sq. in. pressure. After about one and one-half hours two molecular equivalents of hydrogen had been absorbed, and the catalyst was re- [fol. 16] moved by filtration. The filtrate was concentrated *in vacuo* on a steam bath, the residue was dissolved in ethyl acetate and a little ether, and the solution filtered free of a fine suspension and concentrated to dryness *in vacuo*. The residue (4.09 g.) was dissolved in a benzene-pentane (1:1) mixture and subjected to chromatography on 140 g. of acid-washed alumina. The column was eluted with 44 400 ml. portions of benzene-pentane (1:1). The crystalline material (1.91 g., m.p. 121-136°C.) obtained from fractions 4 to 44 was recrystallized successively from ether-pentane, methanol-water, and ether-pentane and dried for eight hours at 95°C. *in vacuo* to give 2α,17α-dimethylandrostan-17β-ol-3-one in the form of colorless plates, m.p. 138.6-142.4°C. (corr.), $[\alpha]_D^{25}=+8.82°$ ±0.2° (1% in chloroform); infrared maxima at 2.92 and 5.85 μ, and a shoulder at 5.86 μ indicating the possible presence of some of the 2β-methyl stereoisomer.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76.
Found: C, 79.10; H, 10.65.

THAT the attached Exhibits C, D and E are photocopies of pages 174, 180 and 182, respectively, of my notebook Man-A kept in the ordinary course of business and in my handwriting. The entries appearing in this notebook record were made prior to December 17, 1956. Exhibits C, D and E show the preparation of 2α,17α-di-

methylandrostan-17β-ol-3-one by the above-described procedure;

And further I say not.

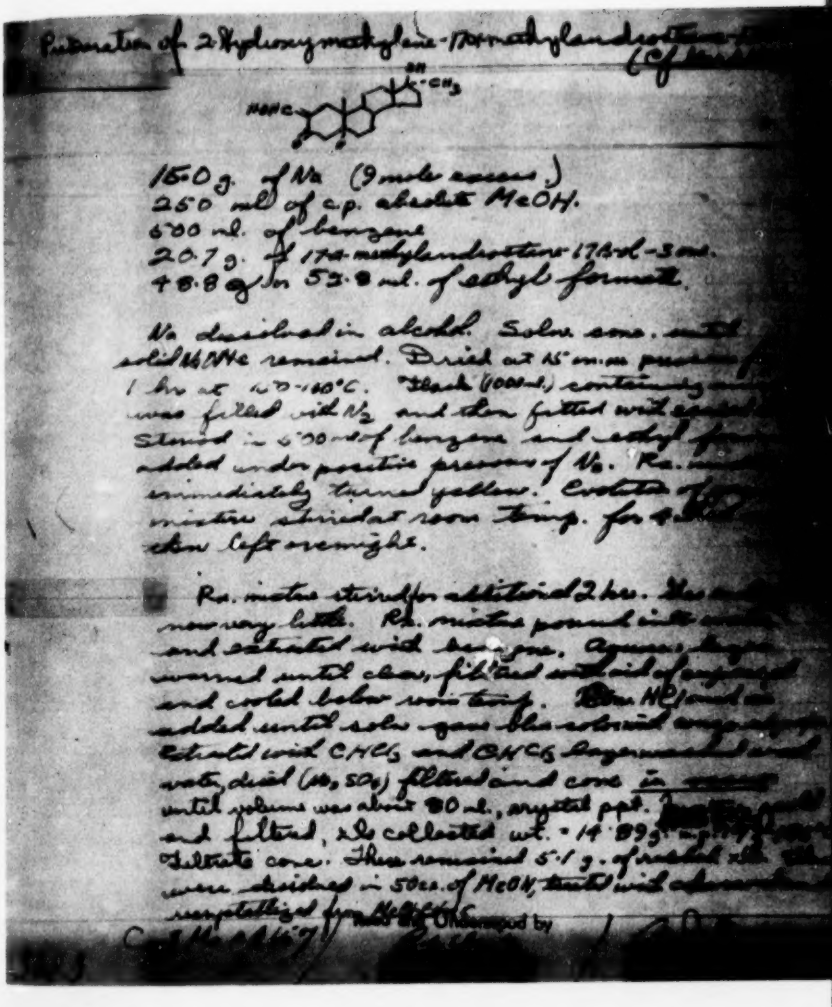
ANDREW JOHN MANSON

Sworn to and subscribed before me this 30th day of March, 1960.

ANNA C. CARD
Notary Public
State of New York
Qualified in Albany County
Commission Expires March 30, 1960

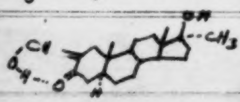
(SEAL)

[fol. 17] EXHIBIT A TO AFFIDAVIT



[fol. 19] EXHIBIT B TO AFFIDAVIT

Preparation of 2-Hydroxymethylene-17α-methylandrostane-17β-ol-3-[illegible]
(Cont'd)



A Sample was prepared as a prospective [illegible]
Rx from Ether-MeOH

Rx	Wt.	m.p.
I	5.00 g.	17[illegible]
II	2.30 g.	175[illegible]
III	0.75	1[illegible]

Sample (0.78 g.) dried at 80°C. [illegible]
a prospective [illegible] sample. After [illegible]
184-192°C.

[redacted] Calc. for $C_{21}H_{32}O_3$ [illegible]

Carbon	75.86	76[illegible]
Hydrogen	9.70	9[illegible]

$[\alpha]_D^{25}$ = +22.3° (1% in $CHCl_3$)
corr. m.p. 185.2 - 190.4°C. [illegible]

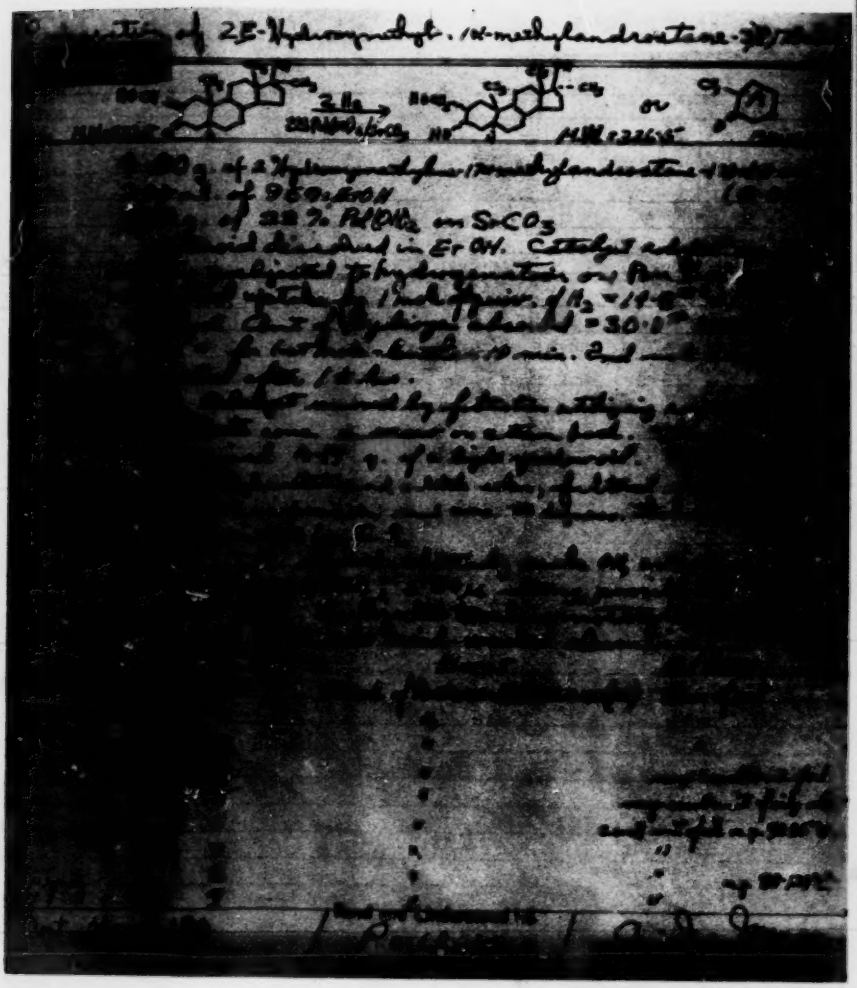
Read and Understood by
Read and [illegible] by

R.O. Clint[illegible] [redacted]

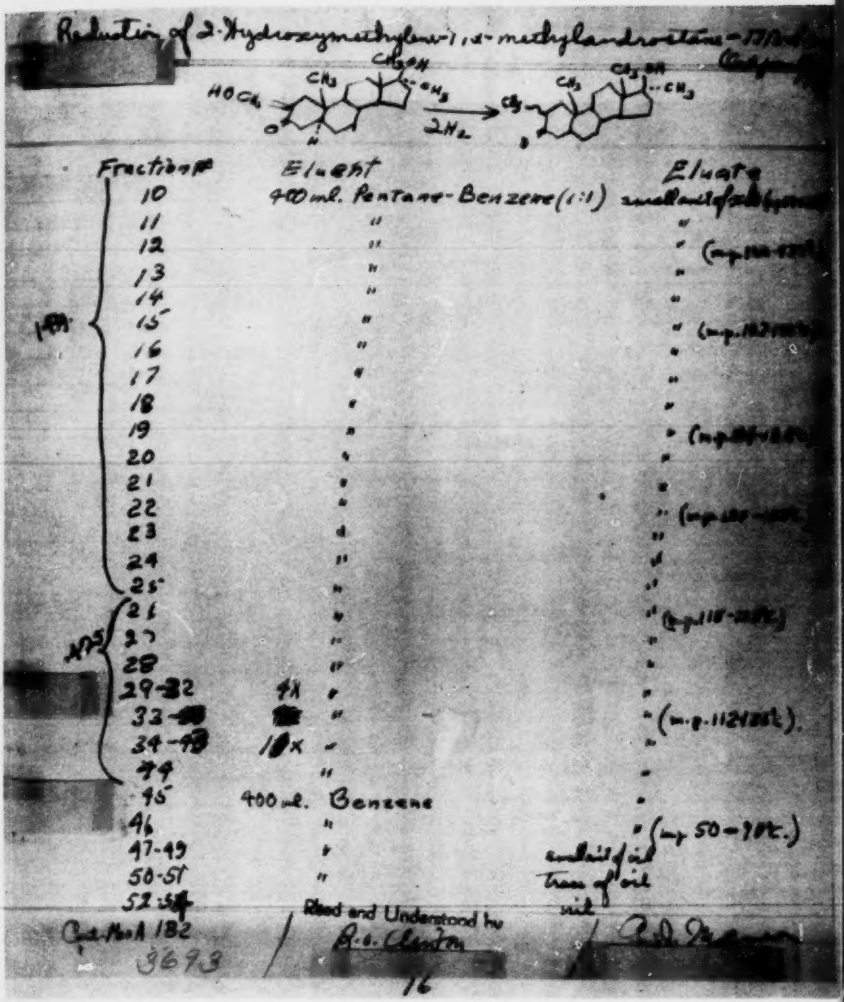
[redacted]

See Man E133 — [illegible]

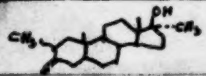
[fol. 21] EXHIBIT C TO AFFIDAVIT



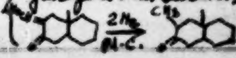
[fol. 23] EXHIBIT D TO AFFIDAVIT



Reduction of 2-Hydroxymethylene-[illegible] -methylandrostane-17β-ol-3-one
(Cmd from Mo. & A180)



{Yanagita and Tsutsaki, J.O.C. 21, [illegible]



Fraction #		Eluent	Eluate
55-56	2X	400ml. Benzene-Ether (9:1)	trace of oil
57-61		"	nil
62		400ml. Benzene-Ether (1:1)	trace of oil
63-65	3X	"	xls. encrusted [illegible]
66-70	5X	"	trace of oil
71-75	5X	"	oil
76		400ml. ETHER	trace of oil
77-78	2X	"	trace of white [illegible]
79-82	4X	"	trace of oil
83-84	2X	"	nil
[illegible]	7X	400ml. ETHER-MeOH (99:1).	small amt of oil
[illegible]-91	5X	"	trace of oil
92-[illegible]	7X	400ml. Ether MeOH (19:1)	small amt of [illegible]

Fractions 4 to 41 were combined affording 1.31 g. of crystalline material m.p. 121-136°C. (50% yield) [illegible] recrystallized from [illegible]-pentane, xls collected, [illegible] m.p. 136-138°C. Recryst. from MeOH-H_2O, crystals [illegible] 0.[illegible] g., m.p. 135-138°C. A third rec., this time from [illegible]-pentane afforded 0.61 g. m.p. 140-142°C. A sample (0.[illegible]) of the [illegible] [illegible] 8 hrs. at 95°C in vacuo & submitted for analysis. A sample was also submitted for I.R.

I.R. Strong OH at 2.92 μ and C=O at 5.85 but [illegible] C=O peak indicating possibly a [illegible] mixture at C_2.

Calc. for $C_{21}H_{34}O_2$, C=79.19; H=10.76; found, C=79.10; H=10.65

[illegible] $[\alpha]_D^{25}$ + 8.9 ± 0.2° (1% in $CHCl_3$); corr. m.p. = 138.6-142.4°C.

WIN 14,835

Read and Understood by R.V. Clinton / A. J. Manson

[illegible]

[fol. 27]

LETTER OF EXAMINER, MAY 24, 1960

Responsive to amendment and affidavit filed April 1, 1960.

Claims 1 and 2 are in the case.

Attention of applicant is called to the fact that claim 1 has been improperly copied from patent No. 2,908,693. See section 1102.01(b), page 157, column 2, paragraph 2 of the MPEP.

The claim should read as follows:

Claim 1:

> A process for the production of a 17α-lower alkyl 2α methyl dihydrotestosterone comprising hydrogenating a 17α-lower alkyl 2-hydroxymethylene dihydrotestosterone in the presence of a hydrogenation catalyst selected from the group consisting of palladium and platinum catalyst.

The rejection in paragraph IV, page 2 of the last Office action, Paper No. 3, is not now applied in accordance with the procedure outlined in section 1101.02(f), pages 153 and 154 of the MPEP, without prejudice to the later application of the reference after the interference is declared, as is set forth in the above section.

(I) Claims 1 and 2 are rejected as being obviously fully met by the Ringold et al I patent, of record, which discloses the instantly claimed processes at column 1, line 34—column 2, line 7 and column 2, lines 23-46. Applicant's affidavit under Rule 204(b) filed April 1, 1960 (Paper No. 4) is insufficient to overcome the effective date of the reference for the following reasons:

1. It fails to disclose any utility for 2α,17α-dimethylandrostan-17β-ol-3-one, the final product allegedly produced.

2. It fails to show that said final product was known to have utility prior to the effective date of the reference. It is noted that the Ringold et al II article, of record, does not show any utility for said final product.

3. It fails to conclusively show that 2α,17α-dimethylandrostan-17β-ol-3-one was in fact produced. Exhibits C, D [fol. 28] and E refer to the product as being ". . . possibly an epimeric mixture at C_2," and do not definitely state that the α-epimer was either produced or isolated. In addition, exhibit E contains the notation "reported J. Org. Chem. *21* 1334 (1956)," which is a reference to the Ringold et al II article, but the analytical data shown in exhibit E (melting point, α_D, etc.) do not agree with those given for 2α,17α-dimethylandrostan-17β-ol-3-one in the aforementioned article.

(II) Claims 1 and 2 are rejected.

The rejection is made *FINAL.*

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS ACTION IS SET TO EXPIRE *JULY 27, 1960.*

L. H. GASTON
Examiner

Approved
For Shortened Period
May 20, 1960
I. G. STONE
Supervisory Examiner

LETTER REQUESTING AMENDMENT, DATED JULY 21, 1960

Hon. Commissioner of Patents
Washington 25, D. C.

Sir:

In response to the Office Letter of May 24, 1960, please amend the above-identified application as follows:

* * * *

For Claim 3, see Rejected Claim 3.

REMARKS

The interview kindly granted by the Examiner on July 12, 1960 to applicant's representatives is acknowledged.

It is believed that the following remarks are in accord with the position taken in behalf of applicant at the interview.

[fol. 29] In view of the objection to Claim 1 as improperly copied from Patent No. 2,908,693, Claim 1 is cancelled without prejudice and rewritten as Claim 3, identical with the claim proposed by the Examiner.

Reconsideration is respectfully requested of the sufficiency of applicant's Affidavit Under Rule 204(b) filed April 1, 1960.

With regard to the question of utility as raised in paragraphs 1 and 2 on page 2 of the last Office Action, it is submitted that applicant has made all of the showing as to utility that should properly be required of him for the purpose of declaration of the interference.

The claim involved, Claim 3, is directed to method subject matter. To be useful under the statute, an invention in method must, of course, produce a useful result, which is not questioned by the Patent Office as the disclosure has apparently been found adequate in this respect. The question now is the technical one of whether there was sufficient knowledge in the art at the time applicant made his invention so that the successful performance of the invention by carrying out the method and producing and analyzing the product could, at that time, be said to have been a useful act. For the following reasons it is submitted it was:—

1. The decision of *In re* Nelson et al. by the Court of Customs and Patent Appeals dated June 14, 1960, also directed to an invention in the steroid field, presented a question of patentability of a compound, said by the applicants to be useful as an intermediate. The Patent Office had taken the position that "since a compound which acts as an intermediate for the production of another compound having no utility can hardly be said to be useful in the sense of the law" (emphasis in the opinion), patentable utility was lacking. The Court, in holding the claims patentable, cited many decisions to the point that no particular degree of utility is required. The cited decisions appear to hold that an invention is useful if

[fol. 30] it is not frivolous, worthless, or detrimental to the well being or injurious to the morals of the public.

2. However, as in the Nelson decision, so here, a finding of utility does not require going that far. Applicant was a member of a research organization engaged in serious steroid research in distinction to research in frivolous, immoral matters of the kind held lacking in utility in the decisions referred to. A supplementary affidavit by the inventor will be filed stating by whom he is employed and the general character of the work he does and was doing at the time he made the present invention. The inventor is presently unavailable, being absent on vacation, but the affidavit will be executed and filed imediately upon his return, about August 1, 1960.

If the principle is to be regarded as established that the degree of utility is immaterial, and the avoidance of deception, immorality and frivolity are the criteria, it would seem clear that applicant's contribution more than satisfies what is needed for a finding of utility.

3. However, apart from the foregoing, there was knowledge in the art inuring to applicant's benefit as to the utility of compounds of the type applicant produced by the method claimed. Thus the Ringold et al. J. Org. Chem. reference referred to describes 2α-methylandrostan-17β-ol-3-one as a tumor inhibitor and that compound differs from the compound produced by the method of Claim 3 only in lacking the 17β-methyl substituent. This presents the question of whether it may properly be presumed that the homologue produced by the method of Claim 3 had the same utility. In non-steroid cases, at least, there is a presumption that adjacent homologues and even remote members of the same homologous series have substantially the same utility. That is the doctrine of the familiar *In re* Hass and *In re* Henze decisions.

[fol. 31] It has been questioned whether that doctrine is applicable in the steroid field because of a greater known unpredictability of compounds in that field. But it is understood that the doctrine is being applied in that field, and if it is, the doctrine, of course,

works both ways. There cannot be a sound presumption which on the one hand weighs against patentability and which on the other hand does not apply with equal force when the opposite conclusion is sought to be drawn from it.

4. Be that as it may, the very homologue with the 17β-methyl substituent which is recited as produced by the process of Claim 3 was known in fact to be a hormone. Ringold et al. (J. Org. Chem.) say: "While anti-tumor screening of the above described 2-methyl hormones is still in progress, Ia and IIa have already been shown to be very effective tumor inhibitors." (underlining added)

Accordingly, it is submitted that at the time applicant made his invention the knowledge in the art was adequate to support a conclusion on applicant's part, under all circumstances, that what he had accomplished by the method of Claim 3 was useful.

Applicant's purpose in adding Claim 3 is to provoke an interference with the Ringold patent. In the event that the Examiner still questions the sufficiency of applicant's Affidavit Under Rule 204(b), and for that reason denies applicant the right to contest the interference with Ringold et al., the Examiner, by that ruling, will have made a determination on the issue of priority as between applicant and Ringold which goes to a very fine distinction on the law of utility in interference practice of the sort which the Examiner thereby in fact will have found has been left open and undecided by the *In re* Nelson decision. The purpose of Nelson et al., like applicant, was to get into an interference, as Nelson et al. also had copied the claims in qeustion from an issued patent, as the opinion [fol. 32] shows. Applicant, having clearly performed the claimed method and produced the claimed compound prior to Ringold is entitled to have the question of priority, including its utility aspect, determined by the Board of Patent Interferences and, if necessary, by appeal to the Court of Customs and Patent Appeals. It is respectfully submitted that under the statute, 35 U.S.C. 135, jurisdiction for the determination of priority is in the Board of Patent Interferences and not in the Primary Examiner.

Without questioning, for the purposes of the present argument, the right of the Commissioner of Patents to delegate authority to the Primary Examiners to determine whether a bona fide interference case is presented which should be transmitted to the Examiner of Interferences for the determination of priority, pursuant to Rules 204 (b) and 131, applicant does very seriously question jurisdiction of Primary Examiners to determine questions of law such as here presented, should the Examiner again reject Claim 3. One of the dissenting opinions in the *In re* Nelson et al. decision, as originally handed down, posed the question as to the effect of that decision on the requirements as to utility in proof of reduction to practice in an interference. We have the same question of proof in applicant's case here involved and it is submitted that it should be decided *inter partes* by the Board of Patent Interferences having statutory jurisdiction in such matters. So far as the Primary Examiner's jurisdiction is concerned, manifestly there is a bona fide interference case which should be transmitted for decision as applicant clearly performed the method, analyzed the product and satisfied what is understood to be the law on the question of utility.

The Examiner also holds the affidavit insufficient as not conclusively showing that 2α,17α-dimethylandrostan-17β-ol-3-one was in fact produced.

Firstly, the Examiner has not denied that applicant has presented adequate evidence that he "hydrogenated a 17α-lower-alkyl 2-hydroxymethylene dihydrotestosterone in [fol. 33] the presence of a hydrogenation catalyst selected from the group consisting of palladium and platinum catalyst." This is all the claim calls for. The product of the process, named only in the preamble of the claim, must follow as an inevitable result of the process, otherwise the claim is indefinite for failure to include necessary reaction conditions for obtaining the product. The patent claims cannot now be challenged in this respect.

Secondly, it is urged, nevertheless, that the product was indeed completely identified as 2α,17α-dimethylandrostan-17β-ol-3-one. Out of an excess of caution common among reputable scientific investigators, applicant indi-

cated the product as "possibly an epimeric mixture at C_2", although it was to be expected that the product would assume largely the stable, equatorial conformation, that is, the α-configuration (see specification, page 2, lines 10-16). In any event, if a mixture of epimers had indeed been produced, it perforce contained some of the α-isomer, and that is all that the claim calls for.

Thirdly, the Examiner's statement that the data shown in Exhibit E do not agree with that given in the Ringold et al. II reference is incorrect. With regard to the melting point data, applicant found m.p. 138.6-142.4°C. and Ringold et al. 151-154°C. Such differences in melting points reported by different investigators for the same substance are not uncommon, and may be explained by such phenomena as polymorphic forms and variations in melting point due to rate of heating and solvent of recrystallization. It is noted also that the Ringold et al. melting points are uncorrected (footnote 6) whereas applicant's melting points are corrected. Attention is also called to the publication of Ringold et al., J. Am. Chem. Soc. *81*, 427-32 (1959) where it is shown (page 430, column 1) that 2α,17α-dimethylandrostan-17β-ol-3-one prepared by the exact procedure here claimed had a melting point of 147-151°. This is in closer agreement with applicant's melting point than that of the product obtained by the older alternative procedure. A photocopy of page [fol. 34] 430 of the newly cited Ringold et al. reference is enclosed herewith.

The Ringold et al. 1959 reference is not a statutory bar as evidenced by the title page (photocopy attached) showing that the journal was issued January 29, 1959, less than one year prior to the filing date of the instant application.

Turning now to the optical rotational data, again, contrary to the Examiner's statement, agreement between Ringold et al. and applicant is excellent. Ringold et al. show $[\alpha]_D = +8°$ and applicant $[\alpha]_D^{25} = +8.82° \pm 0.2°$. Rotations in each case were determined in chloroform. If applicant's product had significant amounts of the β-isomer in it, the rotation would have been quite different. The

difference in rotation between the 2α-methyl and 2β-methyl isomers can readily be calculated from data provided in the publication of Mazur and Sondheimer, J. Am. Chem. Soc. *80*, 5220-9 (1958) where the following data are given:

2α-Methylcholestan-3-one $[\alpha]_D = +32°$ (ρ 0.9 $CHCl_3$) (page 5226)

2β-Methylcholestan-3-one $[\alpha]_D = +86°$ (ρ 0.88 $CHCl_3$) (page 5228)

(Photocopies of pages 5226-8, inclusive of the Mazur et al. reference are attached). Thus it is seen that replacement of a 2α-methyl group by a 2β-methyl group causes a change in rotation of +54°. It can, therefore, be predicted with certainty that 2β,17α-dimethylandrostan-17β-ol-3-one would have an $[\alpha]_D$ value of +62°, assuming that Ringold et al. had the pure 2α-isomer. In any event, the rotation values prove that the product of Ringold et al. and that of applicant are essentially identical.

In view of the foregoing, it is submitted that the present Rule 204(b) Affidavit is entirely sufficient to show completion of the invention prior to the effective date of the Ringold et al. patent, and that the rejection of the [fol. 35] claims as fully met by said patent should be withdrawn and an interference with said patent declared.

Respectfully submitted,

ANDREW JOHN MANSON

By THOMAS L. JOHNSON
His Agent

July 21, 1960

[fol. 37] ATTACHMENT TO LETTER

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PHYSICAL AND INORGANIC CHEMISTRY

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

The Kinetics of Three-step Competitive Consecutive Second-order Reactions[1]

BY W. J. SVIRBELY

RECEIVED JULY 28, 1958

The rate equations for a three-step competitive consecutive second-order reaction of the type $A + B \xrightarrow{k_1} C + E$, $A + C \xrightarrow{k_2} D + E$, $A + D \xrightarrow{k_3} F + E$ have been analyzed in terms of dimensionless variables. Although the general equation obtained is, in principle, solvable it was more convenient and equally instructive to solve the equation for the special case where $k_3 = 2k_2$.

Frost and Schwemer[2] have succeeded in solving the rate equations for competitive consecutive second-order reactions of the type $A + B \xrightarrow{k_1} C + E$, $A + C \xrightarrow{k_2} D + E$ in terms of general variables. The purpose of this investigation was to analyze the rate equations in terms of general variables for three-step competitive consecutive second-order reactions.

The application of the resulting analysis to the alkaline hydrolysis of 1,3,5-tri-(4-carbomethoxyphenyl)-benzene will appear in another paper.

Mathematical Analysis

The reactions to be considered are

$$A + B \xrightarrow{k_1} C + E$$

$$A + C \xrightarrow{k_2} D + E$$

$$A + D \xrightarrow{k_3} F + E$$

The pertinent rate equations for the above steps are

$$\frac{dA}{dt} = -k_1AB - k_2AC - k_3AD \quad (1)$$

$$\frac{dB}{dt} = -k_1AB \quad (2)$$

$$\frac{dC}{dt} = k_1AB - k_2AC \quad (3)$$

$$\frac{dD}{dt} = k_2AC - k_3AD \quad (4)$$

where A, B, C and D are the molar concentrations at any time t, of the corresponding chemical species. If the initial concentrations of the species A and B are A_0 and B_0 respectively, and those of C and D are zero, then combination of equations 1–4 and integration between limits leads to the material balance equation 5, namely

$$A - 2B - 2C - D = A_0 - 2B_0 \quad (5)$$

If the initial concentrations of species A and B are so adjusted that $A_0 = 2B_0$ (equivalent amounts) then equation 5 leads to

$$C = \frac{A - D - 2B}{2} \quad (6)$$

combination of equations 6 and 1 leads to equation 7, namely

$$\frac{dA}{dt} = \left(\frac{3}{2}k_2 - k_1\right)AB + \left(\frac{k_2}{2} - k_3\right)AD - \frac{k_2}{2}A^2 \quad (7)$$

By use of the dimensionless variables α, β and τ and the parameter K, where

$$\alpha = \frac{A}{A_0};\ \beta = \frac{B}{B_0};\ \tau = B_0k_2t;\ K = \frac{k_1}{k_2} \quad (8)$$

equations 7 and 2 become

$$\frac{d\alpha}{d\tau} = \left(\frac{3}{2}K - 1\right)\alpha\beta + \left(\frac{K}{2} - \frac{k_3}{k_2}\right)\alpha\frac{D}{B_0} - \frac{1}{2}K\alpha^2 \quad (9)$$

$$\frac{d\beta}{d\tau} = -K\alpha\beta \quad (10)$$

On dividing equation 9 by equation 10 one obtains

$$\frac{d\alpha}{d\beta} = \left(\frac{2 - 3K}{6}\right) - \frac{D}{2KB_0}\left(\frac{K}{2} - \frac{k_3}{k_2}\right) + \frac{K}{2}\frac{\alpha}{\beta} \quad (11)$$

(1) Presented in part at the Chicago Meeting of the American Chemical Society, September, 1958.

(2) A. A. Frost and W. C. Schwemer, THIS JOURNAL, 74, 1268 (1952).

alytical sample with which this sample was identical in all respects.

(c) *By Hydrogenation of 2α-Methyltestosterone Cycloethylene Ketal*.—The ketal V (130 mg.) was hydrogenated for 5 hr. at 25° and 570 mm. in 20 ml. of methanol over 120 mg. of prehydrogenated 10% palladium–carbon catalyst (uptake 8 ml.). The filtered solution, after the addition of water (5 ml.) and concentrated hydrochloric acid (1 ml.), was boiled for 30 minutes, concentrated *in vacuo* and precipitated with water. Filtration and crystallization from acetone–hexane gave 40 mg. of authentic IIa, m.p. 150–152°.

2α-Methylandrostan-17β-ol-3-one 17-Propionate (IIa Propionate).—A solution of 1 g. of IIa, 3.3 ml. of propionic anhydride and 1.1 ml. of pyridine after being heated for 2 hr. at 90° was cooled and treated with 50 ml. of water. The mixture was heated to hydrolyze excess anhydride, then cooled and extracted with methylene dichloride, the extract being washed successively with dilute hydrochloric acid, bicarbonate and water. Evaporation and crystallization of the residue from hexane gave 900 mg. of IIa propionate, m.p. 119–120°, $[\alpha]_D$ +34°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.61; H, 10.07. Found: C, 76.48; H, 10.01.

IIa Phenylpropionate.—2α-Methyldihydrotestosterone (1 g.) in 5 cc. of cold pyridine was treated with 0.8 g. of phenylpropionyl chloride and the solution then allowed to stand for 18 hr. at room temperature and finally heated for 30 minutes at 90.° The cooled solution was worked up as in the case of the propionate and the residue chromatographed on 50 g. of neutral alumina, the hexane–benzene (1:1 and 2:3) fractions yielding after crystallization from acetone–hexane, 740 mg. of phenylpropionate, m.p. 122–125°, $[\alpha]_D$ +33°, λ_{max} 258 mμ and 268 mμ, log ε 2.28 and 2.28.

Anal. Calcd. for $C_{29}H_{40}O_3$: C, 79.77; H, 9.23. Found: C, 79.80; H, 9.12.

IIa Cyclopentylpropionate.—Cyclopentylpropionyl chloride was substituted for phenylpropionyl chloride in the preparation above. Chromatography and methanol–water crystallization of the hexane–benzene (3:1) fractions gave 2α-methylandrostan-17β-ol-3-one cyclopentylpropionate, m.p. 98–100°, $[\alpha]_D$ +34°.

Anal. Calcd. for $C_{28}H_{44}O_3$: C, 78.45; H, 10.34. Found: C, 78.70; H, 9.96.

2α,17α-Dimethylandrostan-17β-ol-3-one (IIb). (a) *By Oxalate Sequence*.—17α-Methylandrostan-17β-ol-3-one (10 g.) was condensed with excess ethyl oxalate exactly as described for Ia. Acidification of the sodium salt of the 2-ethoxyoxalate gave an amorphous solid which was filtered, washed, dried and treated successively with methyl iodide and sodium ethoxide as in Ia. The crude product (4.0 g.) remaining after reversal of oxalate condensation was chromatographed on 300 g. of neutral alumina. Crystallization of the benzene–ether (19:1) fractions from ether–hexane gave 0.89 g. (9%) of IIb, m.p. 151–154°, $[\alpha]_D$ +8°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.30; H, 10.82.

(b) *By Hydrogenation of 2-Hydroxymethylene Derivative*.—17α-Methylandrostan-17β-ol-3-one (20 g.) in anhydrous thiophene-free benzene (700 ml.) was treated with ethyl formate (60 ml.), sodium hydride (12 g.) and the mixture stirred for 5 hr. under nitrogen. The sodio salt of the hydroxymethylene derivative was filtered, washed first with benzene, then hexane and dried *in vacuo*. Precipitation in dilute cold hydrochloric acid liberated crude 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one (IVb) (20 g.). The filtered, washed and dried product was added to 700 ml. of methanol containing 16 g. of pre-hydrogenated 5% palladium–carbon catalyst and the product hydrogenated at 25° and 570 mm. Hydrogen uptake (1.2 molar equivalents) ceased in 2 hr., the solution was filtered and concentrated to dryness. The residue (negative ferric chloride test) was purified by chromatography on 960 g. of alkaline alumina. The benzene–ether (9:1) fractions crystallized from acetone–hexane to yield 11.08 g. (55%) of IIb, m.p. 147–151°.

2-Hydroxymethylene-17α-methylandrostan-17β-ol-3-one (IVb).—Ethyl acetate crystallization of the crude 2-hydroxymethylene derivative above (preparation of IIb part (b)) gave pure IVb, m.p. 178–180°, $[\alpha]_D$ +38°, $\lambda_{max.}$ 285 mμ, log ε 3.99. In a number of runs the average yield of purified material was 65%.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.71; H, 9.64.

IVb enol acetate, hexane crystallization, m.p. 144–148°, $[\alpha]_D$ +27° (ethanol), λ_{max} 255 mμ, log ε 4.09. *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.49; H, 9.07.

IVb enol propionate, hexane crystallization, m.p. 135°, $[\alpha]_D$ +26° (ethanol), $\lambda_{max.}$ 257 mμ, log ε 4.11. *Anal.* Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.74; H, 9.14.

IVb enol benzoate, acetone–water crystallization, m.p. 188–190°, $[\alpha]_D$ ± 0°, $\lambda_{max.}$ 230 mμ, log ε 4.19. *Anal.* Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.27; H, 8.08.

2-Hydroxymethylene-17α-methyl-19-nortestosterone (IIIa).—17α-Methyl-19-nortestosterone[21] was condensed with ethyl formate as described above. Crystallization from acetone–ether gave the analytical specimen of IIIa, m.p. 146–147°, $[\alpha]_D$ −74°, $\lambda_{max.}$ 252 mμ and 305 mμ, log ε 4.06 and 3.78.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.95; H, 8.86. Found: C, 75.52; H, 8.65.

2-Hydroxymethylene-17α-methyltestosterone (IIIb) was prepared from 17α-methyltestosterone and ethyl formate as described above; analytical sample from acetone–ether, m.p. 179–181°, $[\alpha]_D$ +6°, $\lambda_{max.}$ 251 and 309 mμ, log ε 4.07 and 3.73.

Anal. Calcd. for $C_{21}H_{30}O_3 \cdot {}^1/_2C_3H_6O$: C, 75.16; H, 9.29. Found: C, 74.81; H, 9.08.

2-Hydroxymethylene-17α-methyl-19-norandrostan-17β-ol-3-one (IVa) was prepared from 17α-methyl-19-norandrostan-17β-ol-3-one[22] and ethyl formate as described above. Crystallization from methanol yielded pure IVa, m.p. 196–197°, $[\alpha]_D$ +96°, $\lambda_{max.}$ 281 mμ, log ε 3.96.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 74.87; H, 9.55.

2α-Methyl-3-cycloethylenedioxy-Δ⁵-androsten-17β-ol (V).—A mixture of 2α-methyltestosterone (Ia) (2 g.), ethylene glycol (20 ml.), benzene (100 ml.) and *p*-toluenesulfonic acid·$1H_2O$ (200 mg.) was boiled for 22 hr. with continuous separation of water. The cooled solution, after potassium carbonate wash, was evaporated to dryness. Crystallization of the residue from acetone–hexane yielded 1.1 g. of V, m.p. 173–177°, and a second crop of 400 mg., m.p. 164–171°. Recrystallization from the same solvent gave the pure material, m.p. 175–178°, $[\alpha]_D$ +41° (pyridine), no selective absorption in the ultraviolet.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.11; H, 9.78.

2α-Methyl-3-cycloethylenedioxy-Δ⁵-androsten-17-one (VI).—A stirred solution of 1.5 g. of V, in 20 cc. of pyridine was cooled to 10° and treated under nitrogen, with 900 mg. of chromium trioxide. The mixture was then allowed to stand at room temperature for 18 hr. before being diluted with 100 ml. of ethyl acetate and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue chromatographed on 20 g. of alkaline alumina. The hexane–benzene (1:1) fractions were crystallized from acetone–hexane yielding the 17-ketone VI (930 mg.), m.p. 201–210°. A sample crystallized from acetone to constant melting point exhibited m.p. 206–210°, $[\alpha]_D$ +51° (pyridine).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.92; H, 9.38.

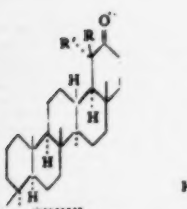
2α-Methyl-17α-ethynyl-3-cycloethylenedioxy-Δ⁵-androsten-17β-ol (VII).—A solution of the preceding ketal-ketone VI (2.0 g.) in 45 ml. of anhydrous benzene was added, under nitrogen, to the solution prepared from dissolving 2 g. of potassium in 40 ml. of *t*-amyl alcohol. A slow current of purified acetylene was passed through the solution for 40 hours, whereupon the solution was poured into ice-water and extracted with benzene. Evaporation of solvent and chromatographic separation of the residue on 100 g. of alkaline alumina gave in the hexane–benzene (2:3) fractions 510 mg. of 17α-ethynyl compound VII. The analytical sample, from acetone–hexane melted at 224–227°, $[\alpha]_D$ −63° (pyridine).

(21) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, This Journal, 76, 4092 (1954).

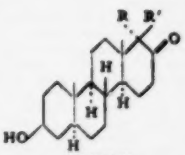
(22) A. Bowers, H. J. Ringold and R. I. Dorfman, *ibid.*, 79, 4556 (1957).

369 3

[fol. 41]



XXXVI
a, R = H, R′ = Me
b, R = Me, R′ = H



XXXVII
a, R = H, R′ = Me
b, R = Me, R′ = H

compound.[29] However, with this pair the usual stability relationship is reversed, the equatorial isomer being the less stable due to interference with the C-12 methylene group. The presently described solvent shift is therefore operative with the less stable isomer XXXVIa, as is also the abnormality of the rotatory dispersion.[29] The last pair in Table III shows that the effect is also observed when comparing rotations measured in chloroform and dioxane. Thus whereas the equatorial methyl compound XXXVIIa shows almost the same rotation in the two solvents, the axial isomer XXXVIIb in dioxane has a markedly lower rotation than in chloroform, the direction of the shift again being opposite to the usual one.[29,a] The magnitude is however less than in the other cases where chloroform was compared with methanol. The observation that the rotations of epimerizable α-methyl ketones are considerably lower in methanol or dioxane than in chloroform seems to be general.

Acknowledgments.—We would like to thank Professor E. R. H. Jones, F.R.S., for giving us advance information prior to publication about the bromination of enol acetates and Professor C. Djerassi for sending us a manuscript of the paper mentioned in footnote 28 before publication. We are also indebted to Dr. S. Pinchas of this Institute for determining the infrared spectra.

Experimental[31]

Direct Methylation of Cholestan-3-one (I). (a) To Give Mainly 2α-Methylcholestan-3-one (II).—A solution of 700 mg. (18 millimoles) of potassium in 35 cc. of *t*-butyl alcohol was added to a boiling solution of 5 g. (13 millimoles) of cholestan-3-one (I) in 50 cc. of benzene and 25 cc. of *t*-butyl alcohol. Methyl iodide (5 cc.) in 5 cc. of benzene was then added and refluxing was continued for 3 minutes. The solution was cooled, ice was added and the product was isolated with ether. The crystalline residue was chromatographed in light petroleum solution on 300 g. of alumina. Elution with light petroleum yielded first 850 mg. of partially crystalline material (fraction A) enriched in 2,2-dimethylcholestan-3-one, then 1.01 g. of 2α-methylcholestan-3-one (fraction B), m.p. 117–119°, and then 482 mg. of material with m.p. 118–121° (fraction C) which by rechromatography was shown to be a mixture of cholestan-3-one and 2α-methylcholestan-3-one. Lastly light petroleum and light petroleum–benzene (9:1 and 4:1) yielded 3.11 g. of unchanged cholestan-3-one (fraction D), m.p. 128–130°.

Crystallisation of fraction B from ether–methanol gave pure 2α-methylcholestan-3-one, m.p. 119–120°, $[\alpha]_D$ +32° (*c* 0.9).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.20; H, 12.20.

Crystallisation of fraction A from ether–methanol gave 0.55 g. of pure 2,2-dimethylcholestan-3-one, m.p. 111–113°, $[\alpha]_D$ +77° (*c* 0.87).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.20; H, 12.33.

(b) To Give Mainly 2,2-Dimethylcholestan-3-one (III).—A solution of 2 g. (51 millimoles) of potassium in 80 cc. of *t*-butyl alcohol was added to a boiling solution of 2 g. (5 millimoles) of cholestan-3-one in 50 cc. of benzene and 25 cc. of *t*-butyl alcohol. Methyl iodide (15 cc.) in 80 cc. of benzene was added and the mixture was boiled under reflux for 1 hr. The product was isolated as previously and was chromatographed in pentane solution on 100 g. of alumina. The first fraction, eluted with pentane, on crystallisation from ether–methanol yielded 1.08 g. of 2,2-dimethylcholestan-3-one, m.p. 111–113°. Identity with the sample prepared by method a was established by non-depression in m.p. on admixture and by infrared comparison. The next fraction, eluted with pentane and pentane–benzene (9:1) gave 120 mg. of 2α-methylcholestan-3-one, which after crystallisation from methanol–ether showed m.p. 119–120°, undepressed with the previously described sample. Lastly, pentane–benzene (9:1 and 4:1) eluted 210 mg. of unchanged cholestan-3-one.

Methylation of Cholestan-3-one (I) via the Ethoxyoxalate IV.—A mixture containing 2 g. of cholestan-3-one, 120 mg. of sodium hydride and 0.66 cc. of ethyl oxalate in 20 cc. of benzene was stirred at room temperature in nitrogen for 76 hr. Ether and water were then added, the aqueous layer was separated, acidified with dilute hydrochloric acid and extracted with ether. This latter ether extract on being dried and evaporated yielded 1.9 g. of the crude ethoxyoxalate IV which was boiled for 16 hr. with 1 g. of anhydrous potassium carbonate and 2 cc. of methyl iodide in 20 cc. of dry acetone. The mixture was cooled and diluted with water and ether. The ether extract was washed with sodium hydroxide solution and water and was then dried and evaporated. The residue was boiled for 3 hr. under reflux with a solution of 5 g. of sodium in 100 cc. of ethanol. The neutral product was isolated with ether and was chromatographed in light petroleum solution on 100 g. of alumina. The fractions eluted with light petroleum and light petroleum–benzene (9:1) gave 900 mg. of 2α-methylcholestan-3-one, m.p. 118–119°. Identity with the above-described sample was established through mixture m.p. determination and infrared comparison.

2α-Methyl-Δ⁴-cholesten-3-one (VII).—A solution of 10 g. of Δ⁴-cholesten-3-one (V) in 50 cc. of benzene was treated with 3.75 cc. of ethyl oxalate and 0.8 g. of sodium hydride and the mixture was allowed to stand at room temperature in nitrogen for 72 hr. Methanol (5 cc.) was added to decompose the unreacted hydride and then ether and water. The aqueous extract was acidified, shaken with ether and the ether extract was dried and evaporated. The resulting crude ethoxyoxalate VI (8.2 g.) was boiled under reflux with 5 g. of anhydrous potassium carbonate and 5 cc. of methyl iodide in 50 cc. of dry acetone for 14 hr. The mixture was cooled, diluted with water and ether and the ether extract was washed with 5% sodium hydroxide solution and water. The oily residue obtained by evaporation of the ether was boiled for 3 hr. with a solution of 5 g. of sodium in 100 cc. of ethanol. Isolation of the neutral product with ether yielded 6.1 g. of a partially crystalline material which was dissolved in light petroleum–benzene (1:1) and chromatographed on 200 g. of alumina. The fractions eluted with light petroleum–benzene (1:1) on crystallization from ether–methanol gave 2.6 g. of 2α-methyl-Δ⁴-cholesten-3-one with m.p. 124–125°. The analytical sample, obtained by further crystallization from ether–methanol, showed m.p. 126–127°, $[\alpha]_D$ +92°, λ_{max} 239 mμ (log ε 4.19), $\nu_{max}^{CS_2}$ 1671 and 1622 cm.⁻¹.

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.20; H, 11.83.

Lithium–Ammonia Reduction of 2α-Methyl-Δ⁴-cholesten-3-one (VII).—A solution of 250 mg. of 2α-methyl-Δ⁴-

(29) T. R. Ames, J. L. Beton, A. Bowers, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 1908 (1954).

(31) Melting points are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina. Rotations were determined at room temperature in chloroform solution. Ultraviolet spectra were measured in 95% ethanol solution on a Unicam Model S.P. 800 spectrophotometer. Infrared spectra were determined on a Perkin-Elmer model 13C single beam spectrophotometer with sodium chloride prism. Analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

cholesten-3-one (VII) in 10 cc. of dry ether was added dropwise with stirring to a solution of 100 mg. of lithium in *ca.* 25 cc. of liquid ammonia during 5 minutes. The mixture was then stirred for another 20 minutes, when 2 g. of ammonium chloride was added. The product was then isolated with ether in the usual way and chromatographed in light petroleum solution on 6 g. of alumina. The fractions eluted with light petroleum and with light petroleum–benzene (9:1) gave 130 mg. of 2α-methylcholestan-3-one (II), which after crystallization from ether–methanol showed m.p. 118–119°. The substance was identical with that prepared previously (mixture m.p., infrared comparison). Further elution with benzene gave fractions which on crystallization from ether–methanol yielded 104 mg. of 2α-methylcholestan-3β-ol (VIIIa), m.p. 139–140°, $[\alpha]_D$ +8° (*c* 1.5).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.51; H, 12.52. Found: C, 83.84; H, 12.39.

Catalytic Hydrogenation of 2α-Methyl-Δ⁴-cholesten-3-one (VII).—A solution of 2 g. of 2α-methyl-Δ⁴-cholesten-3-one in 75 cc. of ethanol was shaken in hydrogen over 200 mg. of a 10% palladium–charcoal catalyst. Uptake of gas stopped after 1.03 molar equivalents of hydrogen had been absorbed. The catalyst and solvent were removed and the residue, dissolved in 50 cc. of absolute ether, was added dropwise to a stirred solution of 1 g. of lithium aluminum hydride in 50 cc. of ether. The mixture was boiled under reflux for 1 hr. and the excess hydride was then decomposed by the careful addition of ethyl acetate. Addition of dilute hydrochloric acid and isolation with ether in the usual way led to 1.98 g. of material which was treated with 4 g. of digitonin in 200 cc. of 90% ethanol. The precipitated digitonide was collected, dissolved in the minimum of pyridine and diluted with ether. The precipitated digitonin was removed by filtration, washed with ether and the ether filtrates were evaporated. The residual crystalline material (568 mg.) on crystallization from ether–methanol yielded 509 mg. of 2α-methylcholestan-3β-ol (VIIIa), m.p. 139–140°, identified with the above-described material through mixture m.p. determination and infrared comparison.

The filtrate obtained after removal of the digitonide was evaporated to dryness, the residue was treated with ether and the excess digitonin was removed by filtration. The ether solution was evaporated and yielded 1.42 g. of crude 2β-methylcoprostan-3α-ol (XIa). A sample on crystallization yielded the pure compound with m.p. 124–126°. The crude material (1.1 g.) dissolved in 50 cc. of acetic acid was oxidized by being allowed to stand for 16 hr. at room temperature with 0.4 g. of chromic acid in 20 cc. of 90% acetic acid. The excess of chromic acid was then decomposed by the careful addition of methanol, water was added and the product was isolated with ether. Crystallization from ether–methanol gave 720 mg. of 2β-methylcoprostan-3-one (X), m.p. 111–112°, $[\alpha]_D$ +30° (*c* 1.1).

Anal. Calcd. for $C_{28}H_{46}O$: C, 83.93; H, 12.08. Found: C, 83.75; H, 12.03.

The analogous oxidation of 500 mg. of the 2α-methylcholestan-3β-ol (VIIIa) obtained from the hydrogenation experiment led to 430 mg. of 2α-methylcholestan-3-one (II), m.p. 119–120°. Identity with the above-described samples was established in the usual way.

When the total hydrogenation product from 2 g. of 2α-methyl-Δ⁴-cholesten-3-one (VII) was chromatographed directly on 100 g. of alumina, the separation was incomplete. After rechromatography, a total of 245 mg. of 2β-methylcoprostan-3-one with m.p. 110–111° and 110 mg. of 2α-methylcholestan-3-one with m.p. 119–120° could be obtained, the former being eluted (with pentane) before the latter.

Reduction of 2α-Methylcholestan-3-one (II) to 2α-Methylcholestan-3β-ol (VIIIa).—A solution of 200 mg. of 2α-methylcholestan-3-one (II) in 20 cc. of ether was added dropwise to 500 mg. of lithium aluminum hydride in 20 cc. of ether. The mixture was boiled under reflux for 2 hr. and then decomposed by the addition of ice and dilute hydrochloric acid. Isolation with ether and crystallization from ether–methanol produced 174 mg. of 2α-methylcholestan-3β-ol (VIIIa), m.p. 139–140°, $[\alpha]_D$ +8° (*c* 1.4), identified with the above-described compound in the usual way. Acetylation (acetic anhydride, pyridine, room temperature, overnight) and subsequent crystallization from methanol yielded the acetate VIIIb with m.p. 107–108°, $[\alpha]_D$ −33° (*c* 1.7).

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.02; H, 11.79. Found: C, 81.01; H, 11.95.

Reduction of 2,3-Dimethylcholestan-3-one (III) to 2,3-Dimethylcholestan-3β-ol (IIIa).—The reduction of 1 g. of 2,3-dimethylcholestan-3-one with 1 g. of lithium aluminum hydride in 70 cc. of ether was carried out as described for the preceding experiment. Crystallization from methanol produced 850 mg. of 2,3-dimethylcholestan-3β-ol (IXa) with m.p. 116–118°, $[\alpha]_D$ +31° (*c* 0.8).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.56; H, 12.58. Found: C, 83.12; H, 12.59.

The acetate IIIb (acetic anhydride, pyridine, room temperature, overnight) on crystallization from methanol showed m.p. 124–126°, $[\alpha]_D$ +19° (*c* 1.2).

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.16; H, 11.87. Found: C, 81.08; H, 11.88.

Reduction of 2β-Methylcoprostan-3-one (X) to 2β-Methylcoprostan-3α-ol (XIa).—2β-Methylcoprostan-3-one (30 mg.) in 10 cc. of ether was reduced with 100 mg. of lithium aluminum hydride in 5 cc. of ether as previously. Crystallization of the product from ether–methanol yielded 66 mg. of 2β-methylcoprostan-3α-ol (XIa), m.p. 124–126°, $[\alpha]_D$ +28° (*c* 1.8).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.51; H, 13.52. Found: C, 83.09; H, 12.26.

The acetate XIb (acetic anhydride, pyridine, overnight at room temperature) on crystallization from methanol showed m.p. 86–87°, $[\alpha]_D$ +78° (*c* 1.1).

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.03; H, 11.79. Found: C, 81.27; H, 11.81.

2-Methyl-Δ¹-cholesten-3-ol Acetate (XII).—A solution of 150 mg. of 2α-methylcholestan-3-one (II) in 20 cc. of isopropenyl acetate was treated with 1 drop of concd. sulfuric acid and the solution was boiled under reflux for 2 hr. The product, isolated with ether in the usual way, was passed in pentane–benzene (9:1) solution through 6 g. of alumina. Crystallization of the eluates from ether–methanol gave 120 mg. of the enol acetate XII with m.p. 93–94°, $[\alpha]_D$ +80° (*c* 1.75), $\nu_{max}^{CHCl_3}$ 1730 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.35; H, 11.46.

2α-Methyl-3β-bromocholestan-3-one (XIII). (a) **By Direct Bromination of 2α-Methylcholestan-3-one (II).**—A solution of 90 mg. of bromine in 3.2 cc. of glacial acetic acid was added dropwise during 10 minutes to a stirred solution of 225 mg. of 2α-methylcholestan-3-one (II) in 15 cc. of acetic acid at room temperature. The mixture was stirred for another 2 hr. and the resulting precipitate was then collected and washed with a little methanol. Crystallization from ether–methanol yielded 116 mg. of the bromo ketone XIII with m.p. 136–137°, $[\alpha]_D$ −20° (*c* 1.06), $\nu_{max}^{CHCl_3}$ 1714 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{47}BrO$: C, 70.11; H, 9.88. Found: C, 70.13; H, 9.89.

(b) **By Bromination of 2-Methyl-Δ¹-cholesten-3-ol Acetate (XII).**—A solution of 40 mg. of bromine in 0.8 cc. of acetic acid was added to 100 mg. of the enol acetate XII dissolved in 18 cc. of acetic acid and 2 cc. of pyridine and the solution was allowed to stand overnight at room temperature. Water and ice were then added, the precipitate was collected, washed with water, dried and crystallized from ether–methanol. This procedure yielded 65 mg. of the 3β-bromo compound XIII, m.p. 136–137°, $[\alpha]_D$ −20° (*c* 0.8). Identity with the sample prepared by method a was established in the usual way.

2-Methyl-Δ¹-cholesten-3-one (XIV).—A solution of 185 mg. of 2α-methyl-2β-bromocholestan-3-one (XIII) in 10 cc. of dimethylformamide containing 1 g. of lithium chloride was boiled under reflux for 2 hr. The product, isolated by means of ether as usual, was triturated with 10 cc. of methanol. The insoluble material was removed by filtration and the filtrate was concentrated to small volume and cooled. The resulting 2-methyl-Δ¹-cholesten-3-one (72 mg.) was obtained as long needles with m.p. 73–74°, $[\alpha]_D$ +62° (*c* 0.9), λ_{max} 241 mμ (log ε 4.02), $\nu_{max}^{CHCl_3}$ 1675 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.39; H, 11.56.

2β-Methylcholestan-3-one (XV).—A solution of 100 mg. of 2-methyl-Δ¹-cholesten-3-one (XIV) in 20 cc. of ethanol

was shaken in hydrogen with 50 mg. of a 10% palladium–charcoal catalyst. Uptake stopped after 1.05 molar equivalents of hydrogen had been absorbed. The catalyst was removed and the filtrate was concentrated to small volume and cooled. The resulting 2β-methylcholestan-3-one (62 mg.) with m.p. 90–92° on further crystallization from ether–methanol yielded the analytical sample with m.p. 96–97°, $[\alpha]_D$ +86° (*c* 0.88). The m.p. was depressed by *ca.* 10° on admixture with a sample of 2α-methylcholestan-3-one.

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.13; H, 12.10.

Isomerization of 2β-Methylcholestan-3-one (XV) to 2α-Methylcholestan-3-one (II).—A solution containing 35 mg. of 2β-methylcholestan-3-one and 0.1 cc. of 20% sulfuric acid in 5 cc. of ethanol was boiled under reflux for 2 hr. Water was added and the product was isolated with ether. One crystallization from ether–methanol gave 2α-methylcholestan-3-one as needles with m.p. 117–119°, undepressed on admixture with an authentic sample (m.p. 119–120°).

2-Methyl-Δ¹-coprosten-3-one (XVIII) and 2α-Methyl-Δ⁴-cholesten-3-one (VII) from 2β-Methylcoprostan-3-one (X).—A solution of 80 mg. of bromine in 1.1 cc. of acetic acid containing a drop of hydrobromic acid (72%) was added to 200 mg. of 2β-methylcoprostan-3-one (X) in 30 cc. of acetic acid. After being allowed to stand at room temperature for 1 hr., the solution was diluted with water and ice and the product was isolated with ether in the usual way. The resulting total brominated product then was dissolved in 10 cc. of dimethylformamide, 1 g. of lithium chloride was added and the solution was boiled for 2 hr. The product, isolated with ether, was dissolved in pentane and chromatographed on 10 g. of alumina. The fractions eluted with pentane–benzene (4:1) on crystallization from methanol gave 43 mg. of 2-methyl-Δ¹-coprosten-3-one (XVIII) as needles with m.p. 96–97°, $[\alpha]_D$ +104° (*c* 0.76), λ_{max} 241 mμ (log ε 4.00), $\nu_{max}^{CCl_4}$ 1671 cm.⁻¹.

Anal. Calcd. for $C_{28}H_{48}O$: C, 84.35; H, 11.63. Found: C, 84.09; H, 11.80.

The fractions eluted with pentane–benzene (1:1) on crystallization from methanol yielded 24 mg. of 2α-methyl-Δ⁴-cholesten-3-one (VII) with m.p. 125–127°, undepressed on admixture with the sample (m.p. 126–127°) described above.

When the bromination of 200 mg. of 2β-methylcoprostan-3-one (X) was carried out as above and the brominated product was crystallized from methanol containing a drop of acetic acid, 45 mg. of 2β-methyl-4β-bromocoprostan-3-one (XVI) with m.p. 126–128°, $[\alpha]_D$ +49° (*c* 0.8), $\nu_{max}^{CCl_4}$ 1730 cm.⁻¹, was obtained.

Anal. Calcd. for $C_{28}H_{47}BrO$: C, 70.11; H, 9.88. Found: C, 70.24; H, 9.91.

The pure bromo ketone XVI (30 mg.) was dehydrobrominated by being boiled under reflux for 2 hr. with 0.5 g. of lithium chloride in 5 cc. of dimethylformamide. Isolation with ether as usual, followed by chromatography on 6 g. of alumina and crystallization of the fractions eluted with pentane–benzene (1:1) from methanol yielded 12 mg. of 2α-methyl-Δ⁴-cholesten-3-one (VII) with m.p. 124–126°. There was no depression on admixture with an authentic sample. No indications of the formation of the Δ¹-isomer XVIII were obtained.

Lithium–Ammonia Reduction of 4-Methyl-Δ⁴-cholesten-3-one (XIX).—A solution of 100 mg. of 4-methyl-Δ⁴-cholesten-3-one (XIX)[9] in 10 cc. of dry ether was added dropwise with stirring to a solution of 100 mg. of lithium in *ca.* 25 cc. of liquid ammonia during 5 minutes. The mixture was then stirred for another 15 minutes, when ice and dilute hydrochloric acid were added and the product was isolated with ether as usual. Crystallization from ether–methanol yielded 71 mg. of 4α-methylcholestan-3-one (XX) with m.p. 121–123°, $[\alpha]_D$ +26° (*c* 1.4); reported[9] m.p. 122–122.5°, 123–124°, $[\alpha]_D$ +25°, +26°.

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.83; H, 12.27.

Catalytic Hydrogenation of 4-Methyl-Δ⁴-cholesten-3-one (XIX).—A solution of 250 mg. of 4-methyl-Δ⁴-cholesten-3-one (XIX)[9] in 50 cc. of ethanol was shaken in hydrogen with 100 mg. of a 10% palladium–charcoal catalyst until uptake ceased, 1.02 molar equivalents of gas being absorbed. The catalyst was removed by filtration and the filtrate was evaporated to small volume and cooled. The precipitate (156 mg., m.p. 87–93°) after three crystallizations from ether–methanol gave 101 mg. of 4β-methylcholestan-3-one (XXI) with m.p. 122–124°. A further purified sample showed m.p. 125–127°, $[\alpha]_D$ +36° (*c* 1.0); reported[9] m.p. 125–127°, $[\alpha]_D$ +36°. There was a *ca.* 20° depression in m.p. on admixture with the 4α-isomer XX.

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 84.02; H, 12.01.

The combined mother liquors were evaporated, dissolved in light petroleum and chromatographed on 10 g. of alumina. The first fractions, eluted with light petroleum, on being seeded and crystallized from ether–methanol gave 25 mg. of 4β-methylcoprostan-3-one (XXII) with m.p. 55–57°, undepressed on admixture with a sample prepared from coprostan-3-one (see below). The later fractions, eluted with light petroleum and light petroleum–benzene, had m.p. 108–118° and could not be purified by crystallization. This material was therefore boiled under reflux for 2 hr. with 25 cc. of ethanol and 0.25 cc. of 20% sulfuric acid. Isolation by means of ether and crystallization from ether–methanol gave 98 mg. of 4α-methylcholestan-3-one (XX) with m.p. 120–122°, undepressed on admixture with the sample obtained by the lithium–ammonia reduction of 4α-methyl-Δ⁴-cholesten-3-one (XIX).

Isomerization of 4β-Methylcholestan-3-one (XXI) to 4α-Methylcholestan-3-one (XX).—A solution of 800 mg. of 4β-methylcholestan-3-one (XXI) in 50 cc. of ethanol containing 0.5 cc. of 20% sulfuric acid was boiled under reflux for 2 hr. Isolation with ether and crystallization from ether–methanol yielded 384 mg. of 4α-methylcholestan-3-one (XX) with m.p. 120–122°, undepressed on admixture with the sample obtained by the lithium–ammonia reduction of 4-methyl-Δ⁴-cholesten-3-one.

4α-Methylcholestan-3β-ol (XXVIa).—A solution of 200 mg. of 4α-methylcholestan-3-one (XX) in 5 cc. of ether was added dropwise to a solution of 200 mg. of lithium aluminum hydride in 10 cc. of ether and the mixture was boiled under reflux for 2 hr. Ice and dilute hydrochloric acid were added and the product was isolated with ether as usual. The resulting material was dissolved in 20 cc. of ethanol and added to 80 cc. of a 2% solution of digitonin in 90% ethanol. The mixture was allowed to stand for 2 hr., the precipitated digitonide was collected, washed with 90% ethanol, dried and dissolved in a few drops of pyridine. Ether (200 cc.) was added, the digitonin was removed and the filtrate was evaporated. Crystallization of the residue from ether–methanol furnished 175 mg. of 4α-methylcholestan-3β-ol (XXVIa) with m.p. 160–163°. The analytical sample showed m.p. 163–164°, $[\alpha]_D$ +27° (*c* 0.8).

Anal. Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52. Found: C, 83.13; H, 12.37.

The acetate XXVIb (acetic anhydride, pyridine, overnight at room temperature) after crystallization from methanol showed m.p. 128–129°, $[\alpha]_D$ +41° (*c* 0.8).

Anal. Calcd. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 81.35; H, 11.67.

4,4-Dimethylcholestan-3β-ol (XXVIIIa).—The reduction was carried out with 500 mg. of 4,4-dimethylcholestan-3-one (XXVII)[9] and 500 mg. of lithium aluminum hydride in 75 cc. of ether as described in the preceding experiment. Separation via the digitonide as before, regeneration and crystallization from methanol yielded 4,4-dimethylcholestan-3β-ol with m.p. 157–158°, $[\alpha]_D$ +11° (*c* 1.45).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.58; H, 12.58. Found: C, 83.02; H, 12.45.

The acetate XXVIIIb (acetic anhydride, pyridine, overnight at room temperature) after crystallization from methanol showed m.p. 138–139°, $[\alpha]_D$ +19° (*c* 1.33).

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.16; H, 11.87. Found: C, 81.37; H, 11.92.

4α-Methyl-Δ⁴-cholesten-3-ol Acetate (XXIX).—A solution containing 300 mg. of 4α-methylcholestan-3-one (XX), 20 cc. of isopropenyl acetate and 1 drop of sulfuric acid was boiled under reflux for 3 hr. The product was isolated with ether, dissolved in pentane–benzene (9:1) and filtered through a column containing 10 g. of alumina. Two crystallizations from ether–methanol yielded 220 mg. of the enol acetate XXIX with m.p. 103–104°, $[\alpha]_D$ +9° (*c* 1.3), $\nu_{max}^{CCl_4}$ 1764 cm.⁻¹.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.60; H, 11.28.

[fol. 47]

APPEAL TO BOARD OF APPEALS, JULY 25, 1960

Hon. Commissioner of Patents
Washington 25, D. C.

Sir:

Applicant hereby appeals to the Board of Appeals from the decision of the principal Examiner finally rejecting Claims 1 and 2.

The Appeal fee of twenty-five dollars ($25.00) is enclosed herewith.

Respectfully submitted,

ANDREW JOHN MANSON

By ELMER J. LAWSON
His Agent

Rensselaer, New York
July 25, 1960

LETTER TO OFFICE, AUGUST 1, 1960

Hon. Commissioner of Patents
Washington 25, D. C.

Sir:

Supplementary to applicant's response dated July 21, 1960, enclosed herewith is an Affidavit by applicant the submission of which was promised on page 3 of said response.

The accompanying Affidavit demonstrates that applicant was not engaged in research of a frivolous kind, but in serious investigations in the steroid field leading to the preparation of a large number of novel steroids. In so doing applicant has contributed to the progress of science and the useful arts.

Respectfully submitted,

ANDREW JOHN MANSON

By THOMAS L. JOHNSON
His Agent

Rensselaer, New York
August 1, 1960

[fol. 48]

AFFIDAVIT OF MANSON, DATED AUGUST 1, 1960

State of New York)
) ss.:
County of Rensselaer)

I, ANDREW JOHN MANSON, being duly sworn, depose and say:

THAT I am a citizen of Canada, residing at Town of North Greenbush, County of Rensselaer, State of New York;

THAT I am the applicant in the above-identified application;

THAT I am an organic chemist by profession (University of New Brunswick, B.S. 1951, and Ph.D. 1954). I worked at Wayne State University in steroid research under the auspices of a post-doctoral grant from the American Cancer Society during 1954-55;

THAT since 1955 I have been employed by Sterling-Winthrop Research Institute, Rensselaer, New York as a research chemist. During this time I have been occupied almost exclusively in the synthesis of novel steroid compounds in research projects designed to produce new medicinal agents in the field of endocrinology. I have in the period of my employment prepared and submitted for testing approximately 80 novel steroid compounds;

And further I say not.

ANDREW JOHN MANSON

Sworn to and subscribed before me this 1st day of August, 1960.

EVA M. REINKE
Notary Public, State of New York
Qualified in Albany County
(SEAL) Commission expires March 30, 1962

[fol. 49]

LETTER OF EXAMINER, AUGUST 30, 1960

Responsive to amendment filed July 22, 1960.

The amendment and affidavit submitted after the final rejection has been entered for purpose of appeal. Claims 2 and 3 are now in the case. Claim 1 having been canceled.

The amendment and affidavit have been carefully considered. However, the amended claims are not considered patentable for the same reasons as set forth under (I) of Paper No. 5.

It is noted that in Ex parte Dickinson, Appeal No. 176-85, Serial No. 695,518 assigned to the same interest as the present application the propriety of requesting an affidavit under Rule 204 (of the nature specified in Rule 131) was held to be a valid one by the Board of Appeals.

Applicant contends that because homologues produced by the process of claim 3 have a known utility, that other compounds described as being produced by a process of claim 3 would be "useful". This has been carefully considered. However, it was held in Blicke v. Treves 44 C. C. P. A., 1957 C. D. 133 that

> "while antispasmodic properties of new material might be reasonably deduced from its similarity to known antispasmodics, they could not be foretold with certainty; hence compound is not of such a nature that it was reduced to practice merely by making it."

Therefore utility of the 17α lower alkyl compounds cannot be foretold with certainty merely because the prior art has held the 17 hydrogen homologue to be effective tumor inhibitors.

The statutory period for response terminates six months from the final rejection. See Rule 192.

M. LIEBMAN
Examiner

[fol. 50]

PETITION TO COMMISSIONER, DECEMBER 19, 1960

Hon. Commissioner of Patents
Washington 25, D. C.

Sir:

This is a petition that the Primary Examiner of Mechanized Division A accept petitioner's affidavits under Rule 204(b) and declare a requested interference.

The invention is in a process for synthesizing an old and known compound. Petitioner's application recognizes the compound as being old. A prior publication of Ringold et al (*J. Org. Chem.* 21; 1333-1335, November 1956) describes the same compound, and also its next adjacent homolog, as being hormones and the homolog as having been shown to be an effective tumor inhibitor; and describes a different synthesis. The Ringold patent, with which interference is sought, describes and claims the same new synthesis that petitioner describes and claims, and also recognizes the resulting compound as being old.

Petitioner's process claim 3 is the one submitted for interference. It is an *Ex parte Card & Card* version of claim 1 of the Ringold patent. No question exists as to the identity of process or as to the sufficiency of claim 3 for interference purposes.

In petitioner's affidavits filed under Rule 204(b) as a *prima facie* showing of invention prior to the effective date (Mexican filing date) of the Ringold patent, it is shown that petitioner carried out the new process prior to that critical date and identified the compound.

The Primary Examiner did not question petitioner's showing that he had carried out the process claimed. He did question petitioner's showing of an identification of the compound produced; but that has been answered, and although the Primary Examiner has not yet ruled that the showing is sufficient in that respect, it is believed that it is, and in any event that question will be disposed [fol. 51] of either by the Examiner's acceptance of the showing or by appeal.

The questions presented by this petition arise from the Primary Examiner's ruling that petitioner's showing is insufficient in not including evidence that the old compound has the utility as a hormone, which it was known in the prior art to have. Petitioner's position on that is threefold.

1. Since the compound is old, and known as a hormone and is a homolog of a known tumor inhibitor, and since the invention is in a new process for its production, petitioner is entitled to contest priority as to the process without showing under Rule 204(b) that prior to the critical date he had tested the compound as a hormone and had proved its known utility.

2. In holding that it is necessary to show proof of utility of the old compound, as a pre-requisite of his right to contest priority as to the process, the Primary Examiner made new law as to what constitutes reduction to practice of a new process for producing an old compound; and, in doing so, the Primary Examiner exceeded his authority under Rule 204(b). Whether or not proof of utility of the old compound is a necessary element in proof of reduction to practice of a new process for its production is a question for decision by the Board of Patent Interferences.

3. As a *prima facie* showing of petitioner's right to contest priority, it is enough that there is a new question of law involved as to the legal consequence of the facts shown, and that petitioner's position on it is a reasonable one. The determination of that new question is vested by law (35 U.S.C. 135) in the Board of Patent Interferences, and the Primary Examiner is without authority to refuse to initiate a priority contest on the basis of his view of how the Board of Patent Interferences should decide that question.

The Board of Appeals has no authority greater than that of the Primary Examiner and cannot properly re-[fol. 52] view on appeal questions the Primary Examiner had no jurisdiction to decide.

This is a matter calling for intervention by the Commissioner of Patents because it involves a new question of the meaning, scope and application of Rule 204(b)

and of Section 135 of the Patent Act, and a question of administration going to the division of authority between the Primary Examiner and the Board of Patent Interferences.

The question differs from that decided in *Ex parte Dickinson et al* Appeal No. 176-85, Serial No. 695,518, because here petitioner has filed affidavits showing facts on which he will rely in support of his claim of priority of invention which obviously are unlike the facts of any decided cases, presenting a new, but nevertheless genuine, question of priority for determination.

This petition neither seeks nor requires either (1) a review of the facts shown by petitioner's affidavits, or (2) a decision on the new question of the law of reduction to practice. It seeks only a directive that the Primary Examiner recognize the genuineness of that question of law and leave its determination to the Board of Patent Interferences.

Respectfully submitted,

ELMER J. LAWSON

December 19, 1960

DECISION OF DIRECTOR OF RESEARCH AND PATENT EXAMINING GROUP I, FEBRUARY 1, 1961

This is a petition to the Commissioner under Rule 181 requesting that the Examiner of Mechanized Division A accept the affidavits filed under Rule 204(b) and declare the requested interference.

This application as filed contained a claim copied from the Ringold patent No. 2,908,693 with a request that an interference be declared with the patent. An affidavit [fol. 53] under Rule 204(b) was filed with the application. The first action rejected the claims over art and stated that an affidavit in the nature of one under Rule 131 was necessary to avoid Ringold. Such an affidavit was filed April 1, 1960. The next action was a final rejection on May 24, 1960. The Examiner pointed out certain de-

fects in the new affidavit and made his rejection on the Ringold patent final. Appeal was taken July 26, 1960 and this petition was filed December 22, 1960.

This petition is directed to appealable subject matter as it relates to the propriety of the rejection of the claims over the Ringold patent. Rule 191. The Examiner's holding that the affidavits are insufficient to warrant an interference with the patent in view of certain alleged defects can only be decided by appeal as it is directly involved in the rejection of the claims.

The petition is accordingly dismissed as drawn to non-petitionable subject matter.

I. G. STONE

Director of Research and
Patent Examining Group 1

EXAMINER'S ANSWER, APRIL 27, 1961

This is an appeal from the final rejection of claims 2 and 3, all the claims in the case.

A correct copy of the appealed claims appears on page 1 of applicant's brief.

The reference of record relied on is:

Ringold et al (I) 2,908,693 Oct. 13, 1959

Reference of record, not relied on, but of interest:

Ringold et al II J. Org. Chem. Nov. 1956 Vol. 21—pages 1333-1335 Copy in Scientific Library

The invention relates to a process for preparing 17 alpha-lower alkyl-2-alpha methyl dihydrotestosterones (claim 3) and specifically a process of making 2 alpha, 17 alpha-[fol. 54] dimethyl androstane-17 beta-ol-3 one (claim 2). The latter compound has been reported in the literature (Ringold et al II article supra) but at that time it had no recognized utility. Claim 3 on appeal, was copied by applicant for purpose of interference with Ringold et al (I) patent No. 2,908,693, cited above; said claim is written in independent form and represents claim 1 of Ringold et al modified to include the limitation of patentee's de-

pendent claim 4. Claim 2, involved in the appeal, has no counterpart in the claims recited in the Ringold et al patent, but is disclosed by Ringold et al. No other references are directly involved in the case.

It should be further noted that although there is no disclosure in the involved application showing the utility of the compounds produced by the processes recited in the appealed claims, this omission is not fatal to applicant's cause since the utility of same was known *prior* to the time the instant application was filed. See column 1, lines 17-26 of the Ringold et al patent which issued October 13, 1959, three months prior to the filing date of the involved Manson application.

The issue revolves around the refusal of the Examiner to permit applicant to enter an interference contest with the Ringold et al patent on the basis of appealed claim 3 and further around the refusal of the Examiner to allow claim 2 over the Ringold et al patent considered solely as a reference. Attention of the applicant is called to the fact that, were claim 2 eventually found to be allowable, even under the present interference practice relating to applicant—patentee situations, 681 O.G. 864 and section 1101.02 of the M.P.E.P., no interference could be declared between applicant and Ringold et al on said claim.

The resolution of the issue on appeal rests on the consideration of the affidavit under Rule 204(b) (in the nature of 131), filed April 1, 1960 by applicant.

[fol. 55] *THE REJECTION*

Claims 2 and 3 are rejected as being obviously fully met by the Ringold et al patent of record which discloses and claims the subject matter of involved claim 3 and discloses the subject matter of involved claim 2. See column 1, line 34 through column 2, line 7, and column 2, lines 23-46.

The above identified affidavit under Rule 204(b) is insufficient to establish priority of invention *relative to the filing date of the patentee*, in accordance with the provisions of said rule for the reasons that:

1. It fails to disclose any utility for 2 alpha, 17 alpha-dimethyl-androstan-17 beta-ol-3-one, the final product, shown in the affidavit.

2. It fails to show that said final product was known to have any utility prior to the effective date of the reference.

(In order to reduce the number of issues on appeal, the holding of insufficiency of the affidavit under Rule 204(b) for reasons given in the last paragraph on page 2, of the final rejection is hereby withdrawn.)

RESPONSE TO APPELLANT'S ARGUMENTS

On page 3 of the brief, it is contended that the claimed process is useful because it affords a known steroid and in re Nelson et al 126 U.S.P.Q. 242 is cited in support of said contention. The portions of said decision cited, (on page 4 of the brief) out of context, do not fully set forth the position of the Court in said case. In addition, in order to establish priority of invention under Rule 204(b) by way of an affidavit in the nature of Rule 131, See #24 therein a specific utility must be shown [,] ^ [accompanied by a successful reduction to practice pursuant to such utility.] This is lacking in the affidavit considered herein. With regard to the Nelson case, [fol. 56] the Court specifically held in 758 O.G. at page 239, column 2, (10) that "in keeping with the policy and spirit of this law (35 U.S.C. 112), *the rule of the Bremner case requires*, as a minimum, that the inventor "indicate" a use for a new composition". In the Nelson case, the Court found a utility in the specification sufficient to satisfy 35 U.S.C. 112. In the instant affidavit, the utility is absent. Applicant therefore argues that he has reduced to practice an old steroid. No utility of the old steroid is shown in the affidavit, however.

[Matter enclosed between brackets erased in copy.]

Applicant therefore contends that the product of the process was known to have utility prior to the effective date of the reference patent and refers to the Ringold et al II article supra. In the paragraph bridging pages 4 and 5 of the brief, applicant concedes an important point; namely, whereas compounds "Ia and IIa have already been shown to be very effective tumor inhibitors", *these compounds are not the compounds produced by the process of the appealed claims nor are these* compounds alleged to be final products shown in the affidavit under Rule 204(b). The most that can be said for the Ringold et al article is, as applicant indicates, the final product is a hormone. Said hormone, as of November 1956 had no recognized utility. The article itself points out that as for antitumor properties, the compounds other than Ia and IIa are in the screening process and this screening "*is still in progress*". Furthermore, the term "hormone" is not in the same category as "paint", "adhesive", "detergent", "insecticide", or "fungicide" as treated in In re Johnson 760 O.G. at page 1042, Section (3), citing In re Nelson et al supra.

Thus, as of November 1956, it could not be urged that the compounds produced by the process of the appealed claims had admittedly utility. ["The implication is clear that, except for the known utility, tests would have been held to be necessary". Blicke v. Treves 1957 C. D. at the top of page 137. No tests are shown in the affidavit, let alone a showing of a successful reduction to practice.]

[fol. 57]

See #24

It is further urged that the compound described by Ringold et al II as having anti-tumor activity differs from the product of claim 3 only in lacking the 17 beta methyl substituent. Thereafter, on pages 5 and 6, applicants advance propositions which are not germane to establishing priority under Rule 204(b) but are directed to patentability, as to the homology doctrine. The doctrines of Hass et al and Henze have no applicability here. [As was stated

[Matter enclosed between brackets erased in copy.]

in Blicke v. Treves supra, at the top of page 138, "it is evident that while the anti-spasmodic properties of a new material might be reasonably deduced from its similarity to known antispasmodics, they could not be foretold with certainty; and that fact is apparent from the record here which shows that appellant and his associates subjected the new material to very extensive tests. For the reasons given, we hold that the instant compounds are not of such a nature *that they were reduced to practice merely by making them.* It remains to be considered whether the tests carried out by or on behalf of appellant were sufficient to effect a reduction to practice". Again, there is nothing in the entire record of this case to demonstrate a sufficient reduction to practice of the compound produced by the process of applicant *prior to the effective date of the reference patent.*]

See #24

Applicant attempts to explain away Blicke v. Treves, supra, on the ground that, there, the products themselves were being claimed while in the instant case, only a process is involved. Again, the Court in said decision clearly stated that "a composition [fol. 58] of matter cannot be a patentable invention unless it has utility, (citing in re Bremner 1950 C.D. 342). Accordingly, the invention of such a composition is not complete unless its utility is either obvious or is established by proper tests, regardless of whether the claims contain any specific reference to utility. In the Bremner case, the Court held, "it was never intended that a patent be granted upon a product, or a process of producing a product, unless such product be useful". This requirement cannot be less stringent when applied to a showing submitted under Rule 204(b) in the nature of an affidavit under Rule 131.

See #24

[Matter enclosed between brackets erased in copy.]

Thus, it is concluded, applicant has not made a prima facie showing of reduction to practice prior to the filing date of the Ringold et al patent.

It is submitted that the rejection is proper and should —sustained.

Respectfully,

L. H. GASTON
Examiner

EXAMINER'S ANSWER, MAY 24, 1962

This application has been remanded by the Board of Appeals to the Primary Examiner in view of termination of the case, In re Dickinson et al, 49 CCPA ——, 133 U.S.P.Q. 39, in the Court of Customs and Patent Appeals.

In view of the decision in the cited case, particular—that portion which states that Blicke v. Treves, 1957 C. D. 133, 112 U.S.P.Q. 472 is clearly distinguishable from the Dickinson case and necessarily from the instant case involving a similar issue, *as to claim 3 only* the Examiner's Answer of April 27, 1961, paper No. 17 is modified to the extent indicated below:

1. On page 4, line 2 after "shown", the comma has been cancelled and the word "therein" has been substituted for the phase "accompanied - - - utility".

[fol. 59] 2. On page 5, first full paragraph, the last two sentences have been deleted.

3. On page 5, second full paragraph, beginning with line 8, the entire language from "as was stated - - - patent" (the latter underlined word on page 6, line three), has been deleted.

4. On page 6, first full paragraph, line 2 after "Treves", the phase ", supra," has been inserted.

Suffice it to say, the Dickinson case supports the position of the Primary Examiner herein since in the language of the Court in 113 U.S.P.Q. at page 43, col. 2, paragraph (5), "In stating in their third affidavit that 'the utility was obvious to us at the time we submitted

the compound for testing which was prior to August 16, 1955,' appellants completed their prima facie case".

For reasons given in the Examiner's Answer, since no utility was shown in the pertinent Manson affidavit involved herein, instant *applicant has not completed his prima facie case.* Nor can a "presumption of utility" *dehors the affidavit,* as is set forth in the paragraph bridging pages 5 and 6 of applicant's brief, replace an allegation of obvious utility or results of actual successful tests *prior to the effective date* of the Ringold patent *in the affidavit itself.*

In order to complete the record and present clear well defined issues to the Board of Appeals, and further, in view of the second full paragraph on page 2 of the Examiner's Answer, it is submitted that for reasons given therein, (attention being now directed to Rosen et al. v. Hjerpe, Interference No. 76,808, patent No. 2,046,951 and Barr et al v. Schildknecht, Interference No. 89,184, patent No. 2,991,278), the only Manson affidavit in issue, paper No. 4 *must* be considered solely as an affidavit under Rule 131 with respect to claim 2 and as an affidavit under Rule 204(b) in the nature of 131, as to claim 3.

Since the same affidavit has been held insufficient under Rule 204(b), a fortiori, it is indeed insufficient under [fol. 60] Rule 131 where the requirements may be more stringent, In re Dickinson supra, and Bliche v. Treves supra, taken together with Ex parte Grosselin 1901 C. D. 248.

Thus, questions a), b) and c) posed on page 9 of the applicant's brief must be answered in the negative.

This application is returned to the jurisdiction of the Board of Appeals.

Respectfully submitted,

M. LIEBMAN
Acting Examiner, Mech A.

LETTER DATED, JUNE 8, 1962

Hon. Commissioner of Patents
Washington 25, D. C.

Sir:

In reply to the Examiner's Answer on Remand, mailed May 24, 1962, there is submitted herewith a Supplementary Affidavit under Rule 204(b) by appellant. This affidavit avers that prior to December 16, 1957, the filing date of Ringold et al. U.S. Patent 2,908,693, the utility of the process of Claim 3 was obvious to appellant. It is submitted that the only deficiency in the Rule 204(b) affidavit, under the criteria set forth in *In re* Dickinson et al., 133 USPQ 39, has now been rectified, that appellant has now completed his prima facie case, and that the application is now in condition for the declaration of interference with the Ringold et al. patent.

In the light of the timing of the *In re* Dickinson et al. decision (handed down by the CCPA on March 22, 1962) and the peculiar situation here where the utility of the claimed process is derived from the prior art [Ringold et al., J. Org. Chem. *21*, 1333 (1956)], it is respectfully submitted that the supplementary affidavit could not have been presented earlier as the need therefor was not apparent to appellant.

[fol. 61] It is respectfully requested that this application be remanded to the Primary Examiner for consideration of the new affidavit and to take the necessary steps to institute interference.

Respectfully submitted,

ANDREW JOHN MANSON

By THOMAS L. JOHNSON
His Agent

June 8, 1962

SUPPLEMENTARY AFFIDAVIT OF MANSON, DATED JUNE 8, 1962

State of New York)
) ss.:
County of Rennsselaer)

I, ANDREW JOHN MANSON, being duly sworn, depose and say:

THAT I am a citizen of Canada, residing at the Town of North Greenbush, County of Rensselaer, State of New York;

THAT I am the applicant in the above-identified U.S. patent application, Serial No. 3693, filed January 20, 1960;

THAT, prior to December 16, 1957, I had read the article by Ringold et al., J. Org. Chem. *21*, 1333 (1956);

THAT, prior to December 16, 1957, the utility of the process of Claim 3 of my application was obvious to me;

And further I say not.

ANDREW JOHN MANSON

Sworn to and subscribed before me this 8th day of June, 1962.

ANNA C. CARD
Notary Public, State of New York
Qualified in Albany County
(SEAL) Commission Expires March 30, 1964

[fol. 62]

LETTER DATED, AUGUST 6, 1962

Hon. Commissioner of Patents
Washington 25, D. C.

Sir:

Pursuant to an interview granted by the Examiner to appellant's representative on or about July 25, 1962, a

supplementary affidavit by appellant is submitted herewith. This affidavit supplements the Supplementary Affidavit under Rule 204(b), dated June 8, 1962, in that it elaborates upon the obviousness of the utility of the claimed process and the utility of the old product produced thereby.

It is submitted that this application is now in condition for favorable reconsideration upon remand from the Board of Appeals (paper No. 27, July 2, 1962).

Respectfully submitted,

ANDREW JOHN MANSON

By THOMAS L. JOHNSON
His Agent

Rensselaer, New York
August 6, 1962

SUPPLEMENT TO SUPPLEMENTARY AFFIDAVIT OF MANSON, DATED AUGUST 6, 1962

County of Rensselaer)
) ss.:
State of New York)

I, ANDREW JOHN MANSON, being duly sworn, depose and say:

THAT I am a citizen of Canada, residing at the Town of North Greenbush, County of Rensselaer, State of New York;

THAT I am the applicant in the above-identified U. S. patent application, Serial No. 3693, filed January 20, 1960;

[fol. 63] THAT, prior to December 16, 1957 the utility of the process of Claim 3 of my application was obvious to me in that it would produce 2α,17α-dimethylandrostan-17β-ol-3-one the utility of which as a hormone analog as

described in the article by Ringold et al., J. Org. Chem. *21*, 1333 (1956) was obvious to me;

And further I say not.

ANDREW JOHN MANSON

Sworn to and subscribed before me this 6th day of August, 1962.

ANNA C. CARD
Notary Public, State of New York
Qualified in Albany County
(SEAL) Commission Expires March 30, 1964

EXAMINER'S ANSWER, AUGUST 27, 1962

This application has again been remanded to the Primary Examiner in view of the communication and supplementary affidavit under Rule 204(b) filed June 11, 1962. The latter affidavit has been further supplemented by an affidavit filed on August 7, 1962.

In the "Examiner's Answer on Remand", dated May 24, 1962, it was noted that the present applicant did not complete his prima facie case under Rule 204(b) since there was no allegation of obvious utility or results of actual successful tests prior to the effective date of the Ringold patent in the affidavit itself. In re Dickinson et al., 1933 U. S. P. Q. 39, was therefore held to support the Examiner's position.

The supplementary affidavit under Rule 204(b), filed June 11, 1962, fails to correct the utility deficiency in the Rule 204(b) affidavit filed April 1, 1960 since no utility for the *final product* produced by the process of claim 3 is alleged therein. The statement to the effect that "the utility of the process of claim 3 * * * was ob- [fol. 64] vious to me" can be given no weight since the product of said process had no known utility prior to the effective date of the Ringold patent.

In a further attempt to complete his prima facie case, as required by In re Dickinson et al., supra, another affidavit supplementing the affidavit of June 11, 1962 was

submitted by applicant on August 7, 1962. This newly presented affidavit states that,

> "prior to December 16, 1957 the utility of the process of claim 3 of my application was obvious to me in that it would produce 2α, 17α-dimethylandrostan-17β-ol-3-one the utility of which as a hormone analog as described in the article by Ringold et al., J. Org. Chem. *21*, 1333 (1956) was obvious to me".

The above equally fails to complete a prima facie case since the term "hormone analog" is not synonymous with any specific utility being inclusive of androgens, estrogens, progestins, andreno-corticoids, etc. As pointed out by the Examiner in his Answer of April 27, 1961, the term "hormone" is not in the same category as "paint", "adhesive", "detergent", etc. as treated in In re Johnson, 127 U. S. P. Q. 216, citing In re Nelson, 126 U. S. P. Q. 242. It should again be noted that the Ringold et al. article, supra, merely establishes the fact that the final product of appealed claim 3 is a hormone.

For the reasons above, it is the judgment of the Examiner that applicant has not completed a prima facie case under Rule 204(b) and therefore the rejection of the claims for reasons given in the Examiner's Answer has not been obivated.

This application is returned to the jurisdiction of the Board of Appeals.

Respectfully submitted,

M. LIEBMAN
Acting Examiner

[fol. 65]

DECISION OF BOARD OF APPEALS, SEPTEMBER 26, 1962

Before Surle and Magil, Examiners-in-Chief, and J. S. Bailey, Acting Examiner-in-Chief.

J. S. Bailey, Acting Examiner-in-Chief.

This is an appeal from the final rejection of claims 2 and 3, the only claims remaining in the application. The rejected claims read as follows:

2. A process for preparing 2α,17α-dimethylandrostan-17β-ol-3-one comprising hydrogenating 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one in the presence of a palladium catalyst.

3. A process for the production of a 17α-lower alkyl 2α methyl dihydrotestosterone comprising hydrogenating a 17α-lower alkyl 2-hydroxymethylene dihydrotestosterone in the presence of a hydrogenation catalyst selected from the group consisting of palladium and platinum catalyst.

The reference relied upon is:

Ringold et al. (I) 2,908,693 Oct. 13, 1959

The following reference of record is referred to by both appellant and the Examiner:

Ringold et al. (II) J. Org. Chem. Nov. 1956 Vol. 21—pages 1333-1335

Claim 3 corresponds to claim 4 of the above Ringold et al. patent and has been made for the purpose of provoking an interference with that patent. The above cited Ringold et al. publication discloses the product of claim 2 (a species within the scope of claim 3) and states that the anti-tumor screening thereof is still in progress while certain other related compounds have already been shown to be very effective tumor inhibitors. Appellant has filed affidavits under the provisions of Rule 204 (b), which, it is urged, establish *prima facie* that he made the invention [fol. 66] defined in claim 3 prior to the filing date of the Ringold et al. patent.

The Examiner has not accepted the affidavits as showing that appelant has made this invention prior to the filing date of the Ringold et al. patent in that they fail to show either that the product of the claimed process was known to have utility or that appellant had established its utility prior to the filing date of the patent. As a consequence, the Examiner has rejected both claims 2 and 3 as obviously fully met by Ringold et al.

It does not appear that the Examiner questions the affidavits filed under the provisions of Rule 204 (b) except as to the showing relative to the utility of the compounds

produced by the process of claim 3. The issue presented is whether the affidavits are sufficient in the respect. Appellant's principal arguments presented in his brief and at the oral hearing may be summarized as follows:

(I) A new and unobvious process of preparing an old compound is inherently useful, even though the compound itself may have no known utility;

(II) The fact that the product of the method claimed has been described as a hormone and the adjacent homologue of the product is also known and has been described as a tumor inhibitor is sufficient to satisfy the statutory requirement of tility; and,

(III) That our conclusion in this case should be governed by the holding of the Court of Customs and Patent Appeals in their decision in *In re* Dickinson and Zenitz, 133 USPQ 39; 780 O. G. 13; 299 F. (2d) 954 and that the showing made in the affidavits filed meet the requirements set forth in this decision as establishing a *prima facie* case of a reduction to practice of the claimed invention.

We shall first consider whether the holding in *In re* Dickinson and Zenitz, *supra*, is controlling on the facts [fol. 67] here. There the court held that by stating in their third affidavit that the utility was obvious to them at the time they submitted the compound for testing and prior to the filing date of the reference patent the appellants there had completed their *prima facie* case. In the third affidavit referred to in that decision, it was stated:

"* * * the utility of ethyl 1-methyl-4-phenlisonipecotate N-Oxide hydrochloride [claim 4] as an analgesic agent was obvious to us prior to the time we made the compound and prior to August 16, 1955, the filing date of Tiffany, U. S. Patent 2,785,168; * * *"

In an affidavit filed August 7, 1962 in this case (Paper No. 28), appellant states:

"THAT prior to December 16, 1957 the utility of the process of Claim 3 of my application was obvious to me in that it would produce 2α,17α-dimethylandro-

> stan-17β-ol-3-one the utility of which as a hormone analog as described in the article by Ringold et al., J. Org. Chem. *21*, 1333 (1956) was obvious to me;"

Appellant contends that the above statement relative to the utility of his process meets the requirements of Rule 204(b) as defined by the court in the above mentioned decision.

We note that the affidavit considered by the court in *In re* Dickinson and Zenitz, *supra*, was that of an analgesic agent. This ascribes a particular physiological effect; that is to say, it was obvious to the affiants that the compound would produce an analgesic effect. Here appellant does not allege that it was obvious to him that the product of the claimed process would have any specified effect but that the obvious utility was "as a hormone analogue." We are constrained to agree with the Examiner that this statement by appellant does not refer to any particular utility or effect. In our opinion this statement in the affidavit merely identifies the class of compounds to [fol. 68] which the product belongs. We find no indication therein that it was obvious to appellant that the product of the process claim would exert any particular effect. For these reasons, it is our opinion that the facts in this case distinguish from those *In re* Dickinson and Zenitz, *supra*, and the affidavits filed under the Rule 204 (b) do not establish a *prima facie* case of a reduction to practice.

Nor, do we believe that the fact that the compounds produced by the process of claim 3 may be hormones and closely related to another hormone shown by the Ringold publication to have utility as a tumor inhibitor can be considered a showing of utility. As pointed out in the Ringold et al. article referred to by appellant and cited above, minor changes in the structure of a steroid may produce profound changes in its biological activity. It is our view that the statutory requirement of usefulness of a product cannot be presumed merely because it happens to be closely related to another compound which is known to be useful.

In support of his contention that the claimed process is inherently useful because it produces a known steroid, ap-

pellant has cited *In re* Nelson et al., 47 CCPA 1031; 758 O. G. 233; 280 F. (2d) 172; 126 USPQ 242; 1960 C. D. 369. We have given careful consideration to appellant's argument on this point but we do not regard this decision applicable to the facts of this case in that the claims were directed to compounds to be used as intermediates in the preparation of other compounds. Since the facts in the *In re* Nelson et al., *supra*, decision are different than those of this case, we are of the view that that decision cannot be held to support the view that a process of preparation of a steroid is useful merely because a product happens to be old. Nor, can this decision support a contention that the steroid produced is useful as an intermediate. This decision does not hold that all compounds are inherently useful as "intermediates."

In Reiners v. Mehltretter, 43 CCPA 1019; 1956 C. D. 399; 711 O. G. 430; 236 F. (2d) 418; 111 USPQ 97, the [fol. 69] Court of Customs and Patent Appeals held that "the literal performance of a claimed method without producing anything useful cannot properly be regarded as a reduction to practice of an invention." As pointed out in Thomas et al. v. Michael et al., 35 CCPA 1036; 1948 C. D. 392; 609 O. G. 696; 166 F. (2d) 944; 77 USPQ 216, where the utility is known, no test is necessary for a reduction to practice. However, we cannot agree that a process is *prima facie* useful merely because the product is disclosed in the literature unless the product was known to be useful.

For the above reasons, we conclude that the affidavit under Rule 204 (b) is not sufficient to establish a *prima facie* case of a reduction to practice of the process of claim 3 and that the rejection of claim 3 is proper and should be sustained. Although claim 2 was not copied from the Ringold et al. patent, we believe that our holding as to claim 3 applies also to claim 2. As was the case in *In re* Hidy & Phillips, 133 USPQ 650; 782 O. G. 16, we believe that claim 2 is actually drawn to the same invention as claimed by Ringold et al., as it differs from claim 4 of that patent in scope only. The rejection of claim 2 will also be sustained.

The decision of the Examiner is affirmed.

AFFIRMED

NOTICE OF APPEAL TO UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS, NOVEMBER 23, 1962

Honorable Commissiobner Of Patents
Washington 25, D. C.

Sir:

You are hereby notified of my appeal to the United States Court of Customs and Patent Appeals from the decision of the Board of Appeals rendered 1962 November 26 rejecting Claims 2 and 3 of my above entitled application and refusing me a patent for the invention set forth therein.

[fol. 70] The following are assigned as reasons of appeal:

1. The Board of Appeals erred in affirming the rejection by the Primary Examiner of Claims 2 and 3 as unpatentable over Ringold et al., U.S. Patent 2 908 693.
2. The Board of Appeals erred in holding the affidavits filed under the provisions of Patent Office Rule 204 (b) insufficient to establish a *prima facie* case of invention of the claimed subject matter by applicant-appellant prior to the filing date of the reference patent.
3. The Board of Appeals erred in failing to hold:

   (I) A new and unobvious process of preparing an old compound is inherently useful, even though the compound itself may have no known utility;

   (II) The fact that the product of the method claimed has been described as a hormone and the adjacent homologue of the product is also known and has been described as a tumor inhibitor is sufficient to satisfy the statutory requirement of utility; and,

   (III) That its conclusion in this case should be governed by the holding of the Court of Customs and and Zenitz, 133 USPQ 39; 780 O.G. 13; 299 F. (2d) 954; 49 CCPA; and that the showing made in the affidavits filed meet the requirements set forth in said

decision as establishing a *prima facie* case of the reduction to practice of the claimed invention.

Respectfully submitted,

ELMER J. LAWSON

ELMER J. LAWSON, Agent

DEAN LAURENCE

DEAN LAURENCE
Attorney for Appeal

[fol. 71]

REQUEST FOR EXTENSION OF TIME AND APPROVAL THEREOF, JANUARY 4, 1963

The Honorable Commissioner of Patents
Washington 25, D. C.

Sir:

Andrew John Manson, by his attorney, hereby petitions that the date when his Petition of Appeal Under CCPA Rule 25 must be filed with the CCPA be extended for approximately 30 days until 1963 February 11.

This extension is sought because the certified copy of the transcript, which must be filed in the CCPA as part of the Petition of Appeal, cannot be ready by the presently required date. Due to delays in transmission of documents from petitioner's agent to the attorney who will handle the CCPA appeal occasioned by the recent Christmas vacation, Petitioner filed his "Request Under Rule 301 To Furnish Certified Transcript" in the Patent Office on 1963 January 4, and normally more time is required to complete a certified transcript.

Extension of time
to Feb 11 1963
Granted
Jan 8—1963
EDWIN L. REYNOLDS
First Assistant Commissioner

It is believed that this extension will afford ample time for the Patent Office photostat department to complete the requested certified transcript and transmit it to the CCPA.

Respectfully,

ELMER J. LAWSON

ELMER J. LAWSON, Agent

DEAN LAURENCE

DEAN LAURENCE

Attorney for the appeal to the CCPA

[fol. 73]

United States Patent Office

2,908,693

Patented Oct. 13, 1959

1

2,908,693

PROCESS FOR THE PRODUCTION OF 2-METHYL-DIHYDROTESTOSTERONES

Howard J. Ringold and George Rosenkranz, Mexico City, Mexico, assignors to Syntex S.A., Mexico City, Mexico, a corporation of Mexico

No Drawing. Application December 16, 1957
Serial No. 702,760

Claims priority, application Mexico December 17, 1956

4 Claims. (Cl. 260—397.4)

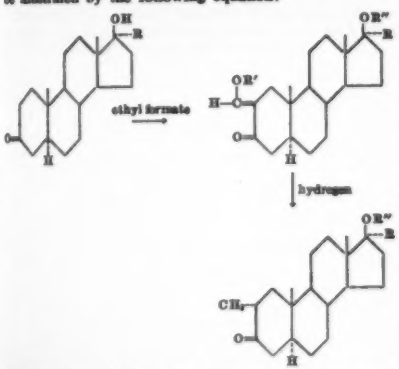
The present invention relates to a novel process for the production of cyclopentanophenanthrene derivatives.

More particularly the present invention relates to a process for the production of 2-methyl dihydrotestosterone derivatives and esters thereof as well as 2-methyl dihydrotestosterone derivatives having a C–17 lower alkyl group. The products of the process of the present invention have a useful high anabolic-androgenic ratio and are especially valuable for treatment of those ailments where an anabolic or antiestrogenic effect together with a lesser androgenic effect is desired.

In our U.S. application Serial No. 636,860, filed January 29, 1957, there is disclosed a process for the production of 2-methyl androstane compounds having a C–17 lower alkyl group involving preparing the corresponding 2-hydroxymethylene derivatives, transformation of these derivatives into 2-methyl-2'-formyl compounds and removal of carbon monoxide to prepare the 2-methyl product.

In accordance with the present invention it has been discovered that 2-methyl androstane compounds or dihydrotestosterone derivatives may be prepared by a simple one step process involving catalytic hydrogenation of the corresponding 2-hydroxymethylene starting material. In its more specific aspects the process therefore involves treating dihydrotestosterone or a 17-lower alkyl dihydrotestosterone as with ethyl formate and sodium hydride to form the corresponding 2-hydroxymethylene derivative and catalytically hydrogenating the 2-hydroxymethylene derivative. Further it has been discovered that catalytic hydrogenation of a 2-acyloxymethylene derivative also produces the desired 2-methyl compounds.

The process of the present invention may therefore be illustrated by the following equation:



In the above equation R represents hydrogen or R represents a lower alkyl group of less than 7 carbon

2

atoms such as methyl, ethyl or propyl. R' represents an acyl group of a hydrocarbon carboxylic acid of 2 to 12 carbon atoms as conventional in esterified steroid alcohols such as acetoxy, propionoxy, benzoyloxy etc. or R' represents hydrogen. R'' represents hydrogen when R is a lower alkyl group and is either hydrogen or an acyl group similar to R' when R is hydrogen.

In practicing the process as outlined above, dihydrotestosterone, or a 17-lower alkyl dihydrotestosterone, such as 17-methyl dihydrotestosterone or 17-ethyl dihydrotestosterone (which may be prepared by treatment of the known testosterone, 17-methyl testosterone or 17-ethyl testosterone with an alkali metal in liquid ammonia for example) are suspended in an inert organic solvent such as benzene and then mixed with ethyl formate and sodium hydride. The mixture is then stirred for a period of time of the order of 5 hours at room temperature and under nitrogen atmosphere. The suspension is then filtered and the mixture of the sodium salt of the desired hydroxymethylene compound is then treated with acid such as hydrochloric acid to precipitate the hydroxymethylene compound.

The hydroxymethylene compound thus prepared may then be conventionally esterified to form a diester of a conventional type as previously set forth when the 17-hydroxy group of the starting compound is secondary or a monoester if the 17-hydroxy group is tertiary (as in 17-lower alkyl derivatives). The hydroxymethylene compound or the ester thereof in organic solvent solution is then hydrogenated in the presence of a hydrogenation catalyst preferably at room temperature and atmospheric pressure until absorption of hydrogen ceased.

Suitable organic solvents for the hydrogenation step are for example lower aliphatic alcohols such as methanol, ethyl acetate, dioxane or acetic acid. Preferable hydrogenation catalysts are palladium or platinum catalysts such as palladium on charcoal or palladium on barium sulfate or platinum oxide. This hydrogenation step produces the corresponding 2-methyl compound from either the ester of or the free hydroxymethylene compound and leaves any 17-ester group intact. The resultant crude 2-methyl products were then purified by chromatography. Where the free hydroxymethylene derivatives were being treated or when a free 2α-methyl product was desired it was found desirable to treat the crude hydrogenation product with alkali prior to chromatography.

The following specific examples serve to illustrate but are not intended to limit the present invention.

Example 1

A suspension of 10 g. of dihydrotestosterone in 500 cc. of anhydrous benzene free of thiophene was mixed with 10 cc. of ethyl formate and 3 g. of sodium hydride and the mixture was stirred for 5 hours under an atmosphere of nitrogen and at a temperature of approximately 25° C. The resulting suspension was filtered, the resulting mixture of the sodium salt of the hydroxymethylene compound and the excess of sodium hydride was washed with benzene and dried. This mixture was slowly added to a vigorously stirred solution of 20 cc. of concentrated hydrochloric acid in 500 cc. of water, and the stirring was continued for 30 minutes at the end of which the precipitate was collected and well washed with distilled water. After drying in vacuo, there was obtained 9.7 g. of 2-hydroxymethylene-dihydrotestosterone.

7 g. of 2-hydroxymethylene-dihydrotestosterone was dissolved in 300 cc. of methanol and mixed with 2.5% of a 10% palladium on charcoal catalyst. The mixture was hydrogenated at approximately 25° C. at atmospheric pressure until the absorption of hydrogen ceased. The catalyst was removed by filtration, 1 g. of potassium hydroxide in 5 cc. of water was added to the solution which

was then kept for 1 hour at room temperature. 2 cc. of acetic acid was added, the solvent was completely removed under reduced pressure, water was added to the residue and the product was extracted with methylene dichloride. The extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. The residue was dissolved in benzene and transferred to a chromatographic column with 125 g. of alkaline alumina. The column was washed with successive fractions of 100 cc. of benzene, whereupon the desired product was eluted from fractions 2 to 6. After evaporating the solvent, the product was crystallized from a mixture acetone-hexane to yield 3.3 g. of pure 2α-methyl-dihydrotestosterone.

Example II

1 g. of 2-hydroxymethylene-dihydrotestosterone, obtained in accordance with Example I, dissolved in 80 cc. of acetic acid was hydrogenated with 1.0 g. of 10% palladium on charcoal catalyst under the conditions described in the previous example. After removing the catalyst by filtration, the solvent was evaporated to dryness under reduced pressure and the residue was mixed with 100 cc. of methanol and 1 g. of potassium hydroxide. The solution was refluxed for 30 minutes and then diluted with water and extracted with methylene dichloride. The extract was washed with water to neutral, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. The residue was dissolved in benzene and chromatographed under the conditions described in Example I. There was thus obtained 2α-methyl-dihydrotestosterone.

Example III

A mixture of 1 g. of 2-hydroxymethylene-dihydrotestosterone, obtained in accordance with the method described in Example I, 10 cc. of pyridine and 2 cc. of acetic anhydride was allowed to react at room temperature for 16 hours and then poured into water. The product was extracted with methylene dichloride and washed consecutively with dilute hydrochloric acid, sodium bicarbonate solution and water, dried and evaporated to dryness under reduced pressure. There was thus obtained the diacetate of 2-hydroxymethylene-dihydrotestosterone.

The diacetate was hydrogenated and then worked up by the methods described in the previous examples, thus producing 2α-methyl-dihydrotestosterone, identical to the one obtained in accordance with such examples.

Example IV

Following the method described in the previous examples, 17α-methyl-dihydrotestosterone was converted into 2α,17α-dimethyl-dihydrotestosterone.

Example V

Following the method described in Examples I, II, and III, 17α-ethyl-dihydrotestosterone was converted into 2α-methyl-17α-ethyl-dihydrotestosterone.

Example VI

A mixture of 1 g. of 2-hydroxymethylene-dihydrotestosterone, obtained in accordance with Example I, 10 cc. of pyridine and 2 cc. of propionic anhydride was allowed to react at room temperature for 16 hours and then poured into water. The resulting suspension was heated for 1 hour on the steam bath to hydrolyze the excess of propionic anhydride, cooled and extracted with methylene dichloride. The extract was consecutively washed with dilute hydrochloric acid, sodium bicarbonate solution and water, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. There was thus obtained the dipropionate of 2-hydroxymethylene-dihydrotestosterone which was treated with hydrogen, in methanol solution, under the conditions described in Example I. When the uptake of hydrogen ceased, the catalyst was filtered and the solution was evaporated to dryness under vacuum. The residue was dissolved in a mixture benzene-hexane, transferred to a chromatographic column with neutral alumina and the product was eluted with mixtures benzene-hexane, gradually increasing the proportion of benzene in the mixture. Crystallization of the eluates from acetone-hexane yielded the propionate of 2α-methyl-dihydrotestosterone.

We claim:

1. A process for the production of compounds selected from the class consisting of 2α-methyl dihydrotestosterone, 17-esters thereof of hydrocarbon carboxylic acids of 2 to 12 carbon atoms and 2α-methyl 17α-lower alkyl dihydrotestosterone comprising hydrogenating the corresponding 2-hydroxymethylene derivatives in the presence of a hydrogenation catalyst selected from the group consisting of palladium and platinum catalyst.

2. The process of claim 1 wherein the starting material is a diester of 2-hydroxymethylene dihydrotestosterone and the product is a 17-ester of 2α-methyl dihydrotestosterone.

3. The process of claim 1 wherein the starting material is 2-hydroxymethylene dihydrotestosterone and the product is 2α-methyl dihydrotestosterone.

4. The process of claim 1 wherein the starting material is a 17α-lower alkyl 2-hydroxymethylene dihydrotestosterone and the product is a 17α-lower alkyl 2α-methyl dihydrotestosterone.

References Cited in the file of this patent

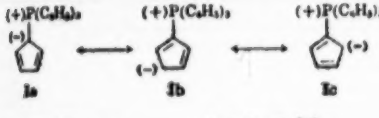
Hogg: J. A. C. S., December 5, 1955, pages 6401–6402.

Communications TO THE EDITOR

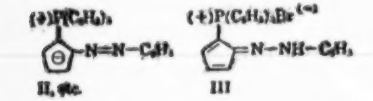
A New Type of Azo Compound by Coupling at the Cyclopentadienide Ring

Sir:

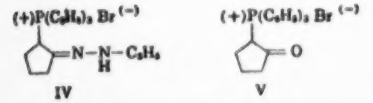
We wish to report the preparation of a new type of azo compound, triphenylphosphonium-(2-phenylazo)cyclopentadienylide [II, deep orange, m.p. 239–240°, from benzene; $\lambda_{max.}^{CH_3CN}$ 220 mμ (ε 49,700), 250 mμ (ε 17,000) and 452 mμ (ε 23,500); band at 7.00 μ but no bands at 3.0 or 4.0–6.6 μ; *Anal.* Calc'd for $C_{29}H_{23}N_2P$: C, 80.9; H, 5.4; N, 6.5; P, 7.2; M.W., 430. Found: C, 80.7; H, 5.8; N, 6.8; P, 7.5; M.W., 413]. II resulted, in high yield, from a coupling reaction between the phosphinemethylene[1] (I) and benzenediazonium chloride in an aqueous-methylene chloride system containing sodium acetate. II formed an orange-red *hydrobromide* best formulated as a derivative of cyclopentadienonephenylhydrazone, III [m.p. 232–233°; $\lambda_{max.}^{EtOH}$ 219 mμ (ε 50,800) 227 mμ (ε 46,200), 259 mμ (ε 17,100), 266 mμ (ε 15,700), 273 mμ (ε 10,100), and 446 mμ (ε 26,700); bands at 3.0 and 6.48 μ (strong); *Anal.* Calc'd for $C_{29}H_{24}BrN_2P$: N, 5.5. Found: N, 5.1].



Ia Ib Ic



II, etc. III



IV V

Catalytic hydrogenation of III in aqueous methanol afforded (2-phenylhydrazonocyclopentyl)triphenylphosphonium bromide [IV, colorless, m.p. 204–205°; $\lambda_{max.}^{EtOH}$ 217 mμ (ε 45,400), 225 mμ (ε 40,600), 269 mμ (ε 20,200), and 277 mμ (ε 20,600); bands at 2.92–3.02, 6.25, and 7.00 μ; *Anal.* Calc'd for $C_{29}H_{25}BrN_2P$: C, 67.6; H, 5.5; N, 5.4; Br, 15.5. Found: C, 67.4; H, 5.8; N, 5.8; Br, 16.0.] An authentic sample of IV was independently prepared from phenylhydrazine and (2-oxocyclopentyl)triphenylphosphonium bromide [V, colorless, m.p. 270–272°; $\lambda_{max.}^{EtOH}$ 217 mμ (ε 38,500), 225 mμ (ε 37,500), 257 mμ (ε 10,100), 266 mμ (ε 9,200), and 275 mμ (ε 6,700); bands at 5.80 and 7.00 μ; *Anal.*, Calc'd for $C_{23}H_{22}BrOP$: C, 65.0; H, 5.2. Found: C, 65.3; H, 5.5]. V was prepared from triphenylphosphine and 2-bromocyclopentanone.

This manifestation of aromaticity in the cyclopentadienide ring opens a route to a family of phosphorus-containing azo compounds of remarkably long wave length absorption (azobenzene: $\lambda_{max.}^{CH_3CN}$ 317 mμ (ε 18,100). The substitution on I occurs at a position which preserves the cyclopentadienide system and which gives rise to the longest of the possible conjugated systems terminating at a phosphorus atom. The dipole moment of II was found[2] to be 6.52 D, as compared with 6.99 D for I.

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK 27, N. Y.

FAUSTO RAMIREZ
STEPHEN LEVY

Received September 4, 1956

(1) F. Ramirez and S. Levy, *J. Org. Chem.*, 21, 488 (1956).

(2) The dipole moments were measured by Prof. M. T. Rogers of Michigan State University and will be the subject of a separate communication.

Steroids. LXXXIII.[1] Synthesis of 2-Methyl and 2,2-Dimethyl Hormone Analogs

Sir:

The discovery that profound changes in biological activity may be effected by removal of the steroid C-10 angular methyl group[2] or by shift of the group from C-10 to C-1[3] prompted us to investigate steroid analogs with additional alkyl substituents in other parts of the molecule. This communication is concerned with the synthesis of a number of 2-methyl and 2,2-dimethyl substituted testosterone and dihydrotestosterone derivatives,[4] compounds of great interest due to the discovery that certain members of this series have been found to be mass-

(1) Paper LXXXII. H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, 21, December 1956.

(2) *Cf.* (a) C. Djerassi, L. Miramontes, and G. Rosenkranz, *J. Am. Chem. Soc.*, 75, 4440 (1953); (b) C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 76, 4092 (1954); (c) C. Huggins, E. V. Jensen and A. S. Cleveland, *J. Exp. Med.*, 100, 225 (1954); (d) A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, 77, 148 (1955).

(3) (a) H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 78, 2477 (1956); (b) C. Djerassi, A. E. Lippman, and J. Grossman, *J. Am. Chem. Soc.*, 78, 2479 (1956).

(4) Presented in part at the 129th meeting of the American Chemical Society, Dallas, April 1956.

ive inhibitors of the development of a transplantable rat mammary tumor.[5]

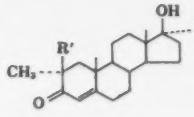
The sodium hydride catalyzed condensation, in benzene solution, of ethyl oxalate with testosterone, androstan-17β-ol-3-one, 17α-methyltestosterone, and 17α-methylandrostan-17β-ol-3-one gave the corresponding 2-ethoxyoxalates (amorphous solids) after acid precipitation of the water-soluble sodio salts. Methylation of the crude free ethoxyoxalates with methyl iodide in boiling acetone containing potassium carbonate gave the corresponding 2-methyl-2-ethoxyoxalates which underwent reversal of oxalate condensation on treatment with ethanolic sodium ethoxide furnishing the 2α-methyl homologs of: testosterone (Ia) (m.p. 155–157°, $[\alpha]_D$ +116°, $\lambda_{max.}$ 242 mμ, log ε 4.19.[6] Found: C, 79.33; H, 10.28). 17α-Methyltestosterone (Ib) (m.p. 150–152°, $[\alpha]_D$ +82°, $\lambda_{max.}$ 240 mμ, log ε 4.21. Found: C, 79.68; H, 10.03). Androstan-17β-ol-3-one (IIa) (m.p. 152–154°, $[\alpha]_D$ +32° (ethanol). Found: C, 78.70; H, 10.77). 2α,17α-Dimethylandrostan-17β-ol-3-one (IIb) (m.p. 151–154°, $(\alpha)_D$ +8°. Found: C, 79.29; H, 10.82).

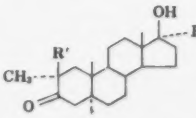
Assignment of the 2-methyl structure in the case of the 3-keto-Δ^4-compounds follows from the established position of oxalate and formate condensation on α,β-unsaturated steroid ketones.[7] The 2α (equatorial) position is assumed from the mode of preparation involving treatment of the final product with strongly alkaline reagent.[8]

That condensation had occurred at C-2 in the dihydrollo series was established by conversion of Ia to its C-3 ketal (2α-methyl-3,3-cyclocthylenedioxy-Δ^5-androsten-17β-ol, m.p. 175–178°, $[\alpha]_D$ +41° (pyridine). Found: C, 76.11; H, 9.78) which after hydrogenation in methanol solution over a palladium-carbon catalyst followed by ketal hydrolysis, gave authentic IIa.

Pyridinium chromate oxidation of the ketal of Ia yielded 2α-methyl-3,3-cyclocthylenedioxy-Δ^5-androsten-17-one (m.p. 206–210°, $[\alpha]_D$ +51° (pyr.). Found: C, 76.92; H, 9 38), which was converted to 2α-methyl-17α-ethinyl-3,3-cyclocthylenedioxy-Δ^5-androsten-17β-ol (m.p. 224–227°, $[\alpha]_D$ −63° (pyr.). Found: C, 77.85; H, 9.31) by treatment with potassium acetylide and 2α-methyl-17α-ethinyltestosterone (Ic) (m.p. 175–178°, $[\alpha]_D$ +3°, $\lambda_{max.}$ 240 mμ, log ε 4.19. Found: C, 81.02; H, 9.33) was derived by ketal hydrolysis. Hydrogenation of Ic over palladium-calcium carbonate in pyridine solution gave 2α-methyl-17α-vinyltestosterone (Id) (m.p. 159–162°, $[\alpha]_D$ +89°, $\lambda_{max.}$ 240 mμ, log ε 4.20. Found: C, 80.54; H, 9.61) while hydrogenation of Ic in dioxane over the same catalyst, interrupted at two moles, gave 2α-methyl-17α-ethyltestosterone (Ic) (m.p. 141–143°, $[\alpha]_D$ +88°, $\lambda_{max.}$ 240 mμ, log ε 4.21. Found: C, 79.95; H, 10.23).

The 2,2-dimethyl compounds were prepared by direct alkylation of androstan-17β-ol-3-one and of 17α-methylandrostan-17β-ol-3-one with excess methyl iodide and potassium *tert*-butoxide in *tert*-butyl alcohol.[9] The mixtures so obtained, in each case, contained about 10% of the 2-monomethyl derivatives IIa and IIb, and 50% of 2,2-dimethylandrostan-17β-ol-3-one (IIc) (m.p. 134–136°, $[\alpha]_D$ +72°. Found: C, 78.84; H, 10.43) and 2,2,17α-trimethylandrostan-17β-ol-3-one (IId) (m.p. 117–120°, $[\alpha]_D$ +53°. Found: C, 78.92; H, 11.12). That these are the 2,2-dimethyl compounds and not the 2,4 or tri- or tetra-methyl derivatives was proven by the following reactions carried out on the C-17 acetate of IIc (m.p. 138–140°). Bromine-acetic acid titration showed uptake of just two moles of bromine. The crystalline dibromo compound (m.p. 180–181°, $[\alpha]_D$ +100°. Found: C, 53.60; H, 6.83; Br, 30.15) on collidine dehydrobromination gave a 4-bromo-Δ^4-3-ketone (2,2-dimethyl-4-bromotestosterone acetate, m.p. 151–153°, $[\alpha]_D$ +82°, $\lambda_{max.}$ 262 mμ, log ε 4.07. Found: Br, 17.92). The monobromo compound [m.p. 146–148°, $[\alpha]_D$ +13° (ethanol). Found: C, 62.59; H, 7.86; Br, 18.47] from treatment of IIc acetate with one equivalent of bromine provided, on collidine dehydrobromination, 2,2-di-





I(a) R = H, R′ = H II(a) R = H, R′ = H
(b) R = Me, R′ = H (b) R = Me, R′ = H
(c) R = —C≡CH, R′ = H (c) R = H, R′ = Me
H
(d) R = —C=CH$_2$, R′ = H (d) R = Me, R′ = Me
(e) R = Et, R′ = H
(f) R = H, R′ = Me

(5) Dr. Charles Huggins, The Ben May Laboratory for Cancer Research, private communication (to be published subsequently).

(6) All melting points are uncorrected. Unless specified otherwise, rotations were determined at 20° in chloroform and the ultraviolet absorption spectra in 95% ethanol. Thanks are due Mr. A. Mijares and Mrs. E. Necoechea for able technical assistance and to Mr. A. Erlin for rotations and spectra.

(7) *Cf.* (a) F. Weisenborn, D. Remy, and T. Jacobs, *J. Am. Chem. Soc.*, **76**, 552 (1954); (b) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Haase, B. J. Magerlein, W. P. Schneider, P. F. Beal, and J. Korman, *J. Am. Chem. Soc.*, **77**, 4438 (1955).

(8) See J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

(9) *Cf.* J. M. Conia, *Bull. soc. chim.*, 000, 943 (1954) for a discussion of related alkylations.

methyltestosterone acetate (If acetate) (m.p. 171–173°, $[\alpha]_D$ +44°, λ_{max}. 240 mμ, log ε 4.19. Found: C, 77.23; H, 9.81).

While anti-tumor screening of the above described 2-methyl hormones is still in progress, Ia and IIa have already been shown to be very effective tumor inhibitors.

RESEARCH LABORATORIES
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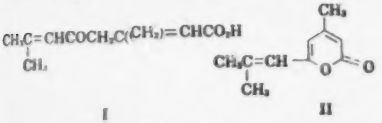
MEXICO, D. F.

H. J. RINGOLD
G. ROSENKRANZ

2-Pyrones. XXIII. 4-Methyl-6-(2′-methylpropenyl)-2-pyrone

Sir:

We wish to report the synthesis of a new ten carbon isoprenoid lactone which is of interest as a simple multiple of senecioic acid in studies of the biosynthesis of cholestrol from acetate.[1-7] 4-Methyl-6-(2′-methylpropenyl)-2-pyrone (II), the lactone of the enol form of γ-senecioylsenecioic acid (I) has been prepared by the acylation of β-methylglu-



I II

taconic anhydride with senecioyl chloride followed by decarboxylative rearrangement. This is a modification of a synthetic route previously described,[8] but successfully applied here for the first time to an aliphatic acid chloride having over four carbon atoms.

A solution of β-methylglutaconic anhydride in pyridine and ether was treated with senecioyl chloride. Ether extraction of the acidified reaction mixture gave a red oil which was decarboxylated by flash distillation and refractionated to give 12% yield of 4-methyl-6-(2′-methylpropenyl)-2-pyrone, m.p. 46.5–47.5°, (*Anal.* Calc'd for $C_{10}H_{12}O_2$: C, 73.11; H, 7.37. Found: C, 73.08; H, 7.37) showing the 2-pyrone carbonyl absorption band at 1730 cm.$^{-1}$ and the trisubstituted ethylenic absorption band at 840 cm.$^{-1}$. Reaction with bromine gave 3-bromo-4-methyl-6-(2′-methyl-2′,3′-dibromopropyl)-2-pyrone, m.p. 119–120°. (*Anal.* Calc'd for $C_{10}H_{11}Br_3O_2$: C, 29.80; H, 2.75. Found: C, 29.88; H, 3.10) showing the 2-pyrone carbonyl absorption band at 1724 cm.$^{-1}$ shifted slightly as with other 3-substituted types.[9]

Acknowledgment. The authors wish to acknowledge support of this research through grants from the National Science Foundation and the United States Public Health Service.

DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES
UNIVERSITY OF LOUISVILLE
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Received October 10, 1956

(1) K. Bloch, L. C. Clark, and I. Harary, *J. Biol. Chem.*, 211, 687 (1954).
(2) J. L. Rabinowitz and S. Gurin, *J. Am. Chem. Soc.*, 76, 5168 (1954).
(3) J. L. Rabinowitz, *J. Am. Chem. Soc.*, 76, 3037 (1954).
(4) H. Rudney, *J. Am. Chem. Soc.*, 77, 1008 (1955).
(5) J. Bonner, *Federation Proc.*, 14, 765 (1955).
(6) H. Rudney and T. G. Farkas, *Federation Proc.*, 14, 737 (1955).
(7) F. Dituri, F. Cobey, J. V. B. Warms, and S. Gurin, *Federation Proc.*, 14, 209 (1955).
(8) R. H. Wiley and N. R. Smith, *J. Am. Chem. Soc.*, 74, 3603 (1952).

(9) R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.*, 78, 2309 (1956).

Ozonolysis of Phenanthrene in Chloroform

Sir:

Schmitt, Moriconi, and O'Connor[1] recently claimed the preparation of the first stable monomeric ozonide of an aromatic hydrocarbon. The material was obtained by the ozonolysis of phenanthrene in either chloroform or acetic acid. It melted at 65–90°. It was assigned a monoozonide structure on the basis of elementary analyses, a Rast molecular weight determination, catalytic hydrogenation to 2,2′-biphenyldicarboxaldehyde, and infrared spectra which showed strong bands in the region 5.7–5.9 μ, which Briner[2] had originally ascribed to ozonides.

Criegee[3] has shown that pure simple ozonides, such as the monoozonide of phenanthrene would be, do not absorb in the 5.6–6.2 μ region, which is the carbonyl region. Briner[4] has recently acknowledged the findings of Criegee and ascribed his results to the formation of aldehydes or ketones during the passage of ozone through the reaction mixture.

We have ozonized phenanthrene (5.9 g.) in chloroform (60 ml.) at −60° and have immediately precipitated the product (7.3 g., 98% yield, m.p. 129–130°) by addition of either ligroin or methanol. Several recrystallizations from benzene by addition of ligroin gave an 80% recovery of material melting at 139–141° (*Anal.* Calcd. for $C_{14}H_{10}O_3$: C,[5] 74.33; H, 4.46; Active O, 7.07. Found: C, 74.58; H, 4.80; Active O, 6.95). The material was

(1) Schmitt, Moriconi, and O'Connor, *J. Am. Chem. Soc.*, 77, 5640 (1955).
(2) Briner, *et al.*, *Helv. Chim. Acta*, 35, 340, 345, 353, 1377, (1952); *Helv. Chim. Acta*, 36, 1166, 1757 (1953); *Helv. Chim. Acta.*, 37, 620, 1558, 1561 (1954); *Compt. rend.*, 234, 1032 (1952); *Compt. rend.*, 237, 504 (1953)
(3) Criegee, Kerckow, and Zinke, *Chem. Ber.*, 88, 1878 (1955).
(4) Briner and Dallwigk, *Compt. rend.*, 243, 630 (1956); *Helv. Chim. Acta*, 39, 1446 (1956).
(5) Schmitt, Moriconi, and O'Connor[1] erred in this calculation. Their product, therefore, analyzed 1% low in carbon.

[fol. 81] REJECTED CLAIMS

2. A process for preparing 2α,17∝-dimethylandrostan-17β-ol-3-one comprising hydrogenating 2-hydroxymethylene-17∝-methylandrostan-17β-ol-3-one in the presence of a palladium catalyst.

3. A process for the production of a 17∝-lower alkyl 2α methyl dihydrotestosterone comprising hydrogenating a 17∝-lower alkyl 2-hydroxymethylene dihydrotestosterone in the presence of a hydrogenation catalyst selected from the group consisting of palladium and platinum catalyst.

[File Endorsement Omitted]

[fol. 82]

[Minute entry of argument and submission—February 7, 1964 (omitted in printing)]

[fol. 83]

IN THE UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS

October Term 1963

Patent Appeal No. 7140

Serial No. 3,693

IN THE MATTER OF THE APPLICATION OF ANDREW JOHN MANSON

OPINION—June 25, 1964

SMITH, Judge.

The single legal issue presented by this appeal is whether an applicant for a patent on a *new process* for making a *known compound* must establish a utility for such *compound*, in order to satisfy the requirements of Rule 204(b) preparatory to having an interference declared between his application and a prior patent.

It is unnecessary to encumber this opinion with any of the technical details of the process covered by appealed claims 2 and 3 of appellant's application.[1] These claims stand rejected as "obviously fully met" by a patent to Ringold et al.[2] Appealed claim 3 corresponds to claim 4 of the Ringold patent and was so written for the purpose of provoking an interference with that patent. Appealed claims 2 and 3 differ only in scope and we shall therefore treat both claims as one for purposes of this opinion.

As required by Rule 204(b), appellant filed certain affidavits which purported to show that he was prima

[1] Serial No. 3,693, filed January 20, 1960, for "Preparation of Organic Compounds."

[2] No. 2,908,693, issued October 13, 1959, entitled "Production of 2-Methyl-Dihydrotestosterones."

[fol. 84] facie entitled to an award of priority of invention relative to the filing date of the Ringold patent. Among other things, these affidavits alleged that the compound produced by the claimed process was known in the art and that its utility was obvious to appellant at the time he invented the process. The examiner, however, took the position that the affidavits were deficient in that they did not clearly show a utility for the compound produced by the claimed process and thus that appellant had not shown that he had made a "useful" invention prior to the filing date of the Ringold patent. This position was summarized by the board as follows:

> It does not appear that the Examiner questions the affidavits filed under the provisions of Rule 204 (b) except as to the showing relative to the utility of the compounds produced by the process of claim 3. The issue presented is whether the affidavits are sufficient in the [this?] respect. * * *

The board, placing its reliance on language found in inter partes interference decisions dealing with what constitutes a reduction to practice of an invention, then concluded:

> * * * we cannot agree that a process is *prima facie* useful merely because the product is disclosed in the literature unless the product was known to be useful.

Thus the board would require that before an applicant may have his claims to a new *process* placed in interference to determine the issue of priority of invention pursuant to 35 U.S.C. 135, he must show that a utility for the *compound* produced by the process was known at the time he invented the process. This requirement cannot be jusified in view of 35 U.S.C. 101. As there defined, a process is a separate category of patentable invention. Clearly, a process which operates as disclosed to produce [fol. 85] a known product is "useful" within the meaning of section 101. To add to this section the further requirement that such a process is "useful" only when a

"use" for a known end product is disclosed seems to us to be an improper arrogation of the authority delegated to Congress by the Constitution. Had such a restriction been intended by Congress, we believe it would have been directly stated either in section 101 or in the definition of a process found in section 100(b). We take the omission of any such requirement to be determinative of the issue here.

We had hoped that our views set forth in *In re Dickenson and Zenitz*, 49 CCPA 951, 299 F. 2d 954, 133 USPQ 39, as to the Commissioner's duties and responsibilities under the statutory provisions and the rules of practice here in issue, would have been considered as determinative of the issue here. While we agree with the board that the *facts* in the *Dickinson and Zenitz* case distinguish it from the *facts* here, we think what was there said is pertinent as to the basic legal right of the appellant to have the issue of priority of invention duly determined as provided in section 135. To the end that there shall be no mistake as to the portions of the *Dickinson and Zenitz* opinion which we think should have been applied in this case, they are quoted as follows (49 CCPA at 957-58):

> There is no question but that under 35 U.S.C. 135, the Commissioner is required to initiate interference proceedings by giving notice to the parties whenever, *in his opinion*, an application would interfere with any pending application or with any unexpired patent.
>
> [fol. 86] Further, under 35 U.S.C. 6, subject to the approval of the Secretary of Commerce, he "may establish regulations, not inconsistent with law, for the conduct of proceedings in the Patent Office." Also, it is equally clear that, unless specifically prohibited by law, the Commissioner may delegate his duties.
>
> On the other hand, in performing his duties, the Commissioner cannot usurp the functions of impinge upon the jurisdiction of the Board of Patent Interferences established by 35 U.S.C. 135.

> In applying these principles to the case at bar, it is obvious that the Commissioner could promulgate a rule to cover the factual situation that is presented in this and similar cases. This he did in establishing Rule 204(b). Also, he could delegate to the Primary Examiner and the Assistant Commissioner his responsibilities under Section 135, and they could decide in the first instance whether a prima facie case had been presented by applicant.
>
> * * * *
>
> The "opinion" of the Commissioner that is required in Section 135 pertains to the factual question of whether the claims of the application would interfere with the claims of the patent, and whether a prima facie case had been alleged. The question of priority is to be determined by the Board of Patent Interferences and such factors, as what is necessary to show reduction to practice in a particular case, come within the exclusive jurisdiction of that board. It should be kept in mind, however, that a patentee ought not to be compelled to go through an interference proceeding without reasonable cause.
>
> Although Rule 204(b) indicates that the required affidavit must be in the nature of that specified in Rule 131, obviously, any provision of Rule 131 which requires more than the statute contemplates in connection with a Rule 204(b) proceeding would not be applicable, as in the case at bar. * * *

In the *Dickenson and Zenitz* case we held that for purposes of a prima facie showing of actual reduction to practice of a chemical compound, the utility requirement of section 101 was satisfied by alleging merely that "the [fol. 87] utility [of the claimed compound] was obvious to us at the time we submitted the compound for testing which was prior to August 16, 1955 [the critical date]." It is our opinion that, if the requirement of a prima facie showing of utility of a claimed compound may be satisfied by the statement that such utility was "obvious" at the time the invention was made, then *a fortiori* the

requirement is satisfied where no question is raised as to the operability of the claimed chemical process to produce a known compound.

It seems clear from the present record that the Patent Office refused to accept appellant's affidavits on the philosophical basis that unless a compound is known to be useful, a process for making the compound is not useful under section 101 and hence not patentable. Thus the case of *In re Wilke and Pfohl*, 50 CCPA 964, 314 F. 2d 558, 136 USPQ 435, cited by appellant and argued by both parties, is not directly controlling here since it dealt with the adequacy of the specification with respect to a disclosure of "how to use" under section 112. *Wilke* is of value, however, in that it indicates the recent thinking of this court with respect to utility issues. In *Wilke*, speaking to the section 112 issue, we said:

> * * * We decline to apply to these process claims the statement in the Bremner case from which the Patent Office has extracted the so-called "rule of Bremner," i.e., that the specification must teach a use for the product of a claimed process. Had this been the intent of Congress, we are certain that it would have been so stated in 35 U.S.C. 112. * * *

[fol. 88] The relevant of this statement to the present case seems clear. If, to be patentable, a process must not only produce a product but a product known or proved to be useful, then it follows that an application for a patent on such a process would have to disclose how to use the product. But the holding in *Wilke* is to the contrary. See also *In re Adams et al.*, 50 CCPA 1185, 316 F. 2d 476, 137 USPQ 333.

In the *Bremner case* [*In re Bremner et al.*, 37 CCPA 1032, 182 F. 2d 216, 86 USPQ 74, 75] this court said, "It was never intended that a patent be granted upon a product, or a process producing a product, unless such product be useful." That this statement is correct with respect to *product* claims is beyond doubt. 35 U.S.C. 101. As to wether a specification must show *how to use* the

product of a claimed *process*, however, our holding in *Wilke* made it abundantly clear that it is not necessary so to do. In the present case, our holding that where a claimed process produces a known product it is not necessary to show utility for the product eradicates, as to process claims, whatever remained of the so-called "rule of Bremner" subsequent to our decision in *Wilke*. See also *In re Szwarc*, 50 CCPA 1571, 319 F. 2d 277, 138 USPQ 208.

Neither the solicitor nor appellant has cited a case, nor have we found any, which is contrary to our present holding. To be sure, in *Petrocarbon Ltd.* v. *Watson*, 247 F. 2d 800, 114 USPQ 94 (D.C. Cir. 1957), the court relied on the *Bremner* case in affirming a rejection of certain chemical process claims. However, as we pointed [fol. 89] out in the *Szwarc* case, supra, the decision made no distinction between product and process claims and was based on the insufficiency of the disclosure of how to use the product produced by the claimed process *as required by section 112*. At any rate, for whatever the *Petrocarbon* case may be said to stand, we have already indicated, at some length, our disagreement with it in both the *Szwarc* case and *In re Nelson et al.*, 47 CCPA 1031, 280 F. 2d 172, 126 USPQ 242, and it would serve no useful purpose to labor the point further here.

The law regarding utility has enjoyed an uncommon stability over the years, in contrast to many other areas in the patent law. In the *Nelson* case, supra, we considered in some depth the ancient and persistent requirement of utility as a condition for patentability. As indicated by the many authorities there discussed, a process is "useful," as a matter of law, if it operates as disclosed to produce its intended result or perform its intended function and if it is not, in operation or result, detrimental to the public interest.

As long ago as 1817, in *Bedford* v. *Hunt*, 3 Fed. Cas. 37 (No. 1217) (C.C.D. Mass.), Justice Story articulated the basis for this general statement, when he said:

> * * * By useful invention, in the statute, is meant such a one as may be applied to some beneficial use in society, in contradistinction to an invention, which

is injurious to the morals, the health, or the good order of society. It is not necessary to establish, that the invention is of such general utility, as to supersede all other inventions now in practice to accomplish the same purpose. It is sufficient, that [fol. 90] it has no obnoxious or mischievous tendency, that it may be applied to practical uses, and that so far as it is applied, it is salutary. *If its practical utility be very limited, it will follow, that it will be of little or no profit to the inventor; and if it be trifling, it will sink into utter neglect. The law, however, does not look to the degree of utility; it simply requires, that it shall be capable of use, and that the use is such as sound morals and policy do not discountenance or prohibit.* * * * [Emphasis added.]

And again in the same year, in *Lowell v. Lewis*, 15 Fed. Cas. 1018 (No. 8568) (C.C.D. Mass.), Justice Story said:

> * * * All that the law requires is, that the invention should not be frivolous or injurious to the well-being, good policy, or sound morals of society. The word "useful," therefore, is incorporated into the act in *contradistinction to mischievous or immoral.* For instance, a new invention to poison people, or to promote debauchery, or to facilitate private assassination, is not a patentable invention. *But if the invention steers wide of these objections, whether it be more or less useful is a circumstance very material to the interests of the patentee but of no importance to the public.* If it be not extensively useful, it will silently sink into contempt and disregard. * * * [Emphasis added.] [8]

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[8] In commenting on this language, one court has said that "A study of the cases reveals that the legal significance of 'useful' in the patent statute differs from the general conversational connotation of the word." *Cusano* v. *Kotler*, 159 F. 2d 159, 162, 72 USPQ 62 (3d Cir. 1947). In that case the court held that the creation of a new game conforms to the patent requirement of being useful.

See also *Callison* v. *Dean*, 70 F. 2d 550, 21 USPQ 240 (10th Cir. 1934), which held that a device which may be used for innocent amusement possesses utility.

This basic rationale has persisted, unchanged, down to the present day, in this court as well as in the District of Columbia Circuit. As recently as 1961, the District Court for the District of Columbia stated, in *Commonwealth Engineering Co.* v. *Ladd*, 199 F. Supp. 51, 131 USPQ 255, 257:

[fol. 91] This Court held in Isenstead v. Watson, 157 F.Supp. 7, 115 USPQ 408, that the term "utility" is a broad term and implies, among other things, capacity to perform the function or attain the result claimed by the applicant in his disclosure. It further held that, in connection with a composition of matter, the test of utility is whether the invention will attain the purpose and will operate as disclosed and claimed by the inventor. Similarly, *in connection with an invention consisting of a process or a method, the term utility must necessarily mean whether the process will operate as claimed and will produce the result intended by the inventor.* [Emphasis added.]

In the present case it is admitted that appellant's claimed process meets these requirements. It operates as claimed and produces the result intended by the inventor. In addition, it has not been shown to be contrary to sound morals and policy. To put it another way, appellant's process *works* and is not alleged to be detrimental to the public interest. Under such circumstances, appellant's affidavits under Rule 204(b) have made a legally sufficient prima facie showing as to his actual reduction to practice of the claimed process prior to the filing date of Ringold. He is, therefore, entitled under section 135 to a determination as to the issue of priority of invention.

The decision of the board is *reversed.*

REVERSED

[fol. 92]

* * * *

WORLEY, Chief Judge, dissenting.

The Patent Office has given Manson an opportunity to show that his product is useful. Although that is his obligation he has been either unable or unwilling to do so. Therefore, the Patent Office quite properly rejected his application and should be affirmed.

I am aware of no authority for the novel proposition that a process which produces a useless product is patentable. Such a premise is wholly contrary to the Constitution and I am satisfied Congress did not intend the statutes enacted thereunder to be so construed.

In *In re Oberweger*, 28 CCPA 749, 115 F.2d 826, 47 USPQ 455, this court quoted with approval an earlier statement from *In re Perrigo*, 18 CCPA 1323, 48 F.2d 965, 9 USPQ 154:

> Neither the Patent Office tribunals nor the court may properly grant patents upon a mere possibility that a device might do the things claimed for it and be useful. There must be definiteness. Neither the Constitution nor the statutes contemplate the granting [fol. 93] of patents upon theories, nor giving a monopoly upon intellectual speculations embodied in devices incapable of scientific analysis.

In *Libbey Owens* v. *Celanese*, 57 USPQ 258, the Sixth Circuit Court of Appeals held:

> Controlling is the fact that such method claims are limited to the use of plastic compositions, with the identical ingredients and in the proportions of the three product claims, which have been already held to be insufficiently disclosed and inoperative, and the process, therefore, lacks the further requisite of utility.

I appreciate the fact than Manson's product is a known compound which may—or may not—someday prove to be useful. However, for his process to possess the requisite statutory utility, it must presently be more than a mere invitation to others to determine that it is useful.

[fol. 94]

IN THE UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS

JUDGMENT—Thursday, June 25, 1964

At a session of said court continued and held at the city of Washington, pursuant to adjournment, on this 25th day of June, A. D. 1964.

Present the Honorable Eugene Worley, Chief Judge, and the Honorables Giles S. Rich, I. Jack Martin, Arthur M. Smith and J. Lindsay Almond, Jr., Associate Judges.

The court was opened for business in due form.

Patent Appeal No. 7140

In the Matter of the Application of
Andrew John Manson

Subject Matter:

Preparation of 2-methyl-17a-lower-alkylandrostan-17b-ol-3-ones.

Serial No. 3,693

Said appeal having heretofore been brought on to be heard before the court and due consideration thereon having been had, it is—

ORDERED that the decision of the Board of Appeals be, and the same is hereby, reversed.

[fol. 95]

[Petition for Rehearing Covering 6 Pages Filed July 20, 1964 Omitted From This Print. It Was Denied, and Nothing More by Order, November 5, 1964]

[fol. 96]

IN THE UNITED STATES COURT OF CUSTOMS AND PATENT APPEALS

* * * *

At a session of said court continued and held at the city of Washington, pursuant to adjournment, on this 5th day of November, A. D. 1964.

Present the Honorable Eugene Worley, Chief Judge, and the Honorables Giles S. Rich, I. Jack Martin, Arthur M. Smith and J. Lindsay Almond, Jr., Associate Judges.

The court was opened for business in due form.

Patent Appeal No. 7140

In the Matter of the Application of
Andrew John Manson

ORDER DENYING PETITION FOR REHEARING—
November 5, 1964

Petition for rehearing having been filed on behalf of the Commissioner of Patents and due consideration thereon having been had, it is—

ORDERED that said petition be, and the same is hereby, denied.

[fol. 97]

[Clerk's Certificate to foregoing transcript omitted in printing.]

[fol. 98]

SUPREME COURT OF THE UNITED STATES

No. ———, October Term, 1964

IN THE MATTER OF THE APPLICATION OF ANDREW JOHN MANSON, PETITIONER

ORDER EXTENDING TIME TO FILE PETITION FOR WRIT OF CERTIORARI—February 3, 1965

UPON CONSIDERATION of the application of the Solicitor General,

IT IS ORDERED that the time for filing a petition for writ of certiorari in the above-entitled cause be, and the same is hereby, extended to and including March 5th, 1965.

/s/ Earl Warren
Chief Justice of the United States.

Dated this 3rd day of February, 1965.

[fol. 99]

SUPREME COURT OF THE UNITED STATES

No. 932, October Term, 1964

EDWARD J. BRENNER, COMMISSIONER OF PATENTS, PETITIONER,

v.

ANDREW JOHN MANSON

ORDER ALLOWING CERTIORARI—April 26, 1965.

The petition herein for a writ of certiorari to the United States Court of Customs and Patent Appeals is granted.

And it is further ordered that the duly certified copy of the transcript of the proceedings below which accompanied the petition shall be treated as though filed in response to such writ.

☆ U. S. GOVERNMENT PRINTING OFFICE: 1965 777994 906